PhD Thesis

Design, synthesis and structural analysis of some podands and polyheteroaromatic macrocyclic compounds

LAR CLAUDIA

President Assoc. Prof. Dr. Cornelia Majdik
Scientific Advisor: Prof. Dr. Ion Grosu
Reviewers: Prof. Dr. Ionel Mangalagiu
           Prof. Dr. Valentin Zaharia
Assoc. Prof. Dr. Eng. Luminita David

Babes-Bolyai Univ., Cluj-Napoca
Babes-Bolyai Univ., Cluj-Napoca
Al. I. Cuza Univ., Iasi
University of Medicine and Pharmacy “Iuliu Hatieganu”, Cluj-Napoca
Babes-Bolyai Univ., Cluj-Napoca

Cluj-Napoca
November 2010
PART I. Design, synthesis and structural analysis of some podands and macrocyclic compounds with pyridine units

I.1. Literature data

I.1.1. General considerations

I.1.2. Strategies for terpyridine synthesis

I.1.3. Coupling strategies of terpyridine derivatives

I.1.4. Supramolecular structures with terpyridine units as base

I.2. Objectives

I.3. Results and discussions

I.3.1. Synthesis and structural analysis of podands with one terpyridine unit

I.3.2. Study of photochemical properties

I.4. Conclusions and perspectives

I.5. Experimental Part

I.5.1. Generalies

I.5.2. Synthesis and analysis of compounds
PART II. Synthesis and structural analysis of new macrocycles with bithiophene units

II.1. Literature data  
II.1.1. Polythiophens functionalised with polyglycols  123  
II.1.2. Synthesis of macrocycles with bithiophene units  125  

II.2. Objectives  129

II.3. Results and discussions  130
   II.3.1. Synthesis of thiophene intermediates  131
   II.3.2. Synthesis of macrocyclic derivatives  135

II.4. Conclusions and perspectives  141

II.5. Experimental part  143
   II.5.1. Generalities  143
   II.5.2. Synthesis and analysis of compounds  144

GENERAL CONCLUSIONS  153

Appendix 1. List of new synthesized compounds  155

Appendix 2. List of publications/posters  159
Introduction

Heterocyclic chemistry had a fast development due to its wide applications in supramolecular chemistry, and also because of its utility in material sciences. Of these, a special importance gained the heterocycles containing nitrogen (and oxygen) atoms, an example in this regard are terpyridine derivatives or oxazines, compounds that open the perspective of synthesizing and studying new molecular assemblies. 2,2′:6′,2″-Terpyridines show a very rich coordination chemistry, mainly due to affinity for a wide variety of transitional metals cations but also of other metals. Because of these properties, different metalo-supramolecular structures have been obtained with distinct photophysical, photochemical, electrochemical, catalytical and magnetic properties. Also, the compounds where used in obtainment of nanostructures (ex. rotaxans, pseudorotaxans, molecular machines, etc). Interesting properties present the heterocycles containing sulphur, especially thiophene whose contribution to semiconductor polymers is well-known.

The results of research presented in thesis are divided in two main parts and include synthesis, structural analysis and properties of some new nitrogen and sulphur containing aromatic heterocycles. In the first part are presented the results obtained in synthesis and analysis of some new terpyridine derivatives. Are included the informations concerning new terpyridine substrates, precursors in the coronands and cryptands synthesis (is presented some literature data about the

study of the terpyridinic derivatives and also the original contributions brought by this thesis in the field of synthesis and structural analysis of these compounds). Are also discussed the attempts made in order to obtain new macrocycles with terpyridinic units, the synthesis methods and the structural analysis of the obtained compounds.

In the second part are presented the main results obtained in synthesis, structural analysis and properties of some bithiophene derivatives, precursors in the synthesis of supramolecular compounds. Also, the synthesis methods for two new macrocycles with a bithiophenic unit are presented.
PART I

Design, synthesis and structural analysis of some podands and macrocyclic compounds with pyridine units
I.2. Objectives

The objective of this part is the synthesis of compounds containing at least one terpyridine unit, precursors in the synthesis of macrocycles. The methods used to obtain macrocycles (coronands, cryptands, etc) starting from these podands are presented. These type of compounds shows coordinative properties, especially a high affinity for the transitional-metals cations and for cations of metals from the rare earth elements. Due to this properties, can be obtained various metalo-supramolecular structures which may present distinct photophysical, photochemical, electrochemical, catalytical and magnetical properties. Moreover, the supramolecular structures have a well defined stereochemistry, which show a great importance, especially when the structure-property relationship is considered. In Scheme 14 is shown the way of obtaining the target podands (intermediates in the macrocyclization reactions), proposed for characterisation and structural analysis.

![Scheme 14](image-url)
I.3. Results and discussions

It was proposed a plan that suppose obtainement of some monoterpyridinic structures functionalized with different groups (type III), step followed by macrocyclization process (type II)\textsuperscript{6,7} and, at final step, will be used different coupling methods to obtain the desired structures of type I. The retrosynthetic scheme is presented below (\textbf{Scheme 19}).

\begin{minipage}{\textwidth}
\centering
\includegraphics[width=\textwidth]{Scheme19.png}
\end{minipage}

\textbf{Scheme 19}

\begin{itemize}
\item \textsuperscript{7} Hamann, C.; Kern, J. M.; Sauvage, J. P. \textit{Inorg. Chem.} 2003, 42, 1877-1883.
\end{itemize}
I.3.1. Synthesis and structural analysis of podands with terpyridine unit

The starting materials used to obtain terpyridine compounds were benzaldehyde and 2-acetylpyridine derivatives. To obtain monoterpyridine 48, was used 4-bromobenzaldehyde and 2-acetylpyridine.\(^8\) The reaction took place in basic conditions, at reflux for two days (Scheme 20) when the desired compound yielded in 65%.

![Scheme 20]

This compound is known in literature data,\(^8\) its structure was confirmed by spectroscopic and mass spectrometry data.

The compound 48 was used with success to obtain N,N-dioxide derivative 49 in presence of m-chloroperbenzoic acid, at room temperature and using DCM as solvent (Scheme 21). Derivative 49 is an important key intermediate for obtaining different terpyridine structures, because N-O group is an orto-directing group, which favours the new substituent to be located in orto position related to nitrogen atom. So, using a Reissert-Henze\(^9\) type reaction, with trimethylsilylcyanide and acetyl chloride, from compound 49 was obtain 6,6”-dicyano monoterpyridine 50 (Scheme 21) in a good yield (50%). The structure of this compound was identified by NMR analysis (proton and carbon) and is identical with the literature data.\(^8\)

---

\(^8\) Han, F. S.; Higuchi, M.; Kurth, D. G. *Org. Lett.* 2007, 9, 559-562.

The –CN group located on the pyridine structure, can be easily transformed in different other functional groups, allowing this compound to be considered a very important precursor to attain many functionalized terpyridine systems.

Thus, using derivative 50 as starting material was tried different methods to obtain some terpyridine derivatives\textsuperscript{10,11} which can allow further (using different ligands) the synthesis of some new supramolecular assemblies (cryptands and/or coronands).

Firstly, was obtained 4‘-(4-bromophenyl)-2,2′:6′,2″-terpyridin-6,6″-dicarboxylic acid 51 following a literature procedure.\textsuperscript{12,13} This compound, further led to formation of diacid chloride 52 (Scheme 22).\textsuperscript{14}

\[ \text{Scheme 21} \]

\[ \text{Scheme 22} \]

To our knowledge, compounds 51 and 52 have not being reported in literature till now. Here, they are presented and fully analysed for the first time. The structure of derivative 51 was resolved based on proton (Figure 13) and carbon NMR analysis and confirmed by mass spectrometry.

![NMR Spectrum](image)

**Figure 13.** $^1$H NMR fragment spectrum of compound 51 (300 MHz, DMSO $d_6$)

In $^1$H NMR spectrum (Figure 13), the $H_3$ and $H_5$ protons give a singlet at $\delta = 8.89$ ppm; this signal is overlapped with signal gave by the $H_5$, $H_5^-$ protons. Superimposed signals appear also in the case of $H_4$, $H_4^-$ and $H_3$, $H_3^-$ protons in region 8.16-8.25 ppm.
Diacide chloride 52 was obtained from diacide 51 in reaction with thionyl chloride (SOCl₂), at reflux for two hours, the yield of this derivative being very good (77%). The structure of this compound was investigated by NMR spectroscopy (¹H and ¹³C) and mass spectrometry. The ¹H NMR spectrum of compound 52 (Figure 16) shows a doublet for H₃ and H₄ protons at δ = 8.95 ppm. At δ = 8.91 ppm was identified the signal for H₃' and H₅, while the most shielded protons are those on phenyl nuclei. Complete analysis for this compound was possible using also 2D-analysis (COSY).

Figure 16. ¹H NMR fragment spectrum of compound 52 (300 MHz, CDCl₃)
Diester 53 (Scheme 23)\(^{15}\) was obtained using dicarboxylic acid 51 as starting material. Also, this compound is for the first time presented here, its structure being identified and confirmed by NMR spectroscopy and mass spectrometry.

Scheme 23

In the mass spectrum of diester 53 (Figure 20) can be observed molecular peak corresponding to [M+H]\(^+\) at \(m/z = 504.1\) and 506.1 respectively; to [M+Na]\(^+\) at \(m/z = 526.1\), 528.1 and also [M+K]\(^+\) at \(m/z = 542.1\) and 544.1 respectively.

Figure 20. Mass spectrum (MALDI+/DCTB) fragment of 53

The compound 53 was reduced to its alcohol 54 using NaBH₄, in anhydrous ethanol (Scheme 24), following a procedure described in literature. The obtained compound was identified and analyzed by NMR spectroscopy (¹H NMR (Figure 21) and APT) but also by mass spectrometry.

Scheme 24

Figure 21. ¹H NMR fragment spectrum of compound 54 (300 MHz, DMSO d₆)
The molecular ion peak \([\text{M+H}]^+\) of 54 (Figure 22) can be observed in mass spectrum at \(m/z = 448.3\) and 450.3 respectively; \([\text{M+Na}]^+\) at \(m/z = 470.3\) and 472.3 but also \([\text{M+K}]^+\) at \(m/z = 486.3\) and 488.3.

![Mass spectrum](image)

**Figure 22.** Mass spectrum (MALDI+/DCTB) fragment for compound 54

Starting from alcohol 54, was obtained derivative 55,\(^\text{15}\) in good yields (Scheme 25); its structure was identified by NMR spectroscopy (Figure 23) and mass spectrometry.

![Scheme 25](image)
Figure 23. $^1$H NMR fragment spectrum of compound 55 (300 MHz, CDCl$_3$)

In $^1$H NMR spectrum of 55 was observed a singlet at 8.71 ppm corresponding to H$_{3,5}$; phenyl protons give AB system at 7.75 ppm; also H$_{3,3''}$ give a doublet 8.57 ppm, at 7.88 ppm appear one triplet for H$_{4,4''}$ and one doublet at 7.52 ppm for H$_{5,5''}$. Methylene protons (-CH$_2$-Br) gave a singlet at 4.68 ppm.

Also, were obtained two series of terpyridine podands (precursors in macrocyclization reactions); general scheme is presented below (Scheme 32) and reaction conditions are gathered in Table 1.
Most of these compounds are new, their structure being resolved by NMR spectroscopy and mass spectrometry. Their general data are presented in experimental part.

### Tabel 1. General reaction conditions for terpyridine derivatives 65-71

<table>
<thead>
<tr>
<th>Compound</th>
<th>65</th>
<th>66</th>
<th>67</th>
<th>68</th>
<th>69</th>
<th>70</th>
<th>71</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
<td>A(R₁=H)</td>
</tr>
<tr>
<td></td>
<td>B(R₂=CN)</td>
<td>B(R₂=CN)</td>
<td>B(R₂=CN)</td>
<td>B(R₂=CO₂H)</td>
<td>B(R₂=CO₂H)</td>
<td>B(R₂=CO₂H)</td>
<td>B(R₂=CO₂H)</td>
</tr>
<tr>
<td>Reaction conditions</td>
<td>NaOH</td>
<td>NH₂OH</td>
<td>Me₂OH</td>
<td>m-CPBA</td>
<td>Me₃SiCN</td>
<td>CH₂COCl</td>
<td>AcOH</td>
</tr>
<tr>
<td></td>
<td>DCM</td>
<td>r.t.</td>
<td>DCM</td>
<td>DCM</td>
<td>DCM</td>
<td>DCM</td>
<td>HCl</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>reflux</td>
</tr>
<tr>
<td>Yield (%)</td>
<td>65A (49%)</td>
<td>66A (74%)</td>
<td>67A (37 %)</td>
<td>68A (66%)</td>
<td>69A (72 %)</td>
<td>79 %</td>
<td>84 %</td>
</tr>
<tr>
<td>Literature data</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>12</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

I.3.2. Photochemical properties

#### 3.2.1. UV-Vis studies

For derivatives 48-60 were inregistered UV-Vis spectra using CH₃CN as solvent (Figure 31) keeping the same concentrations for all samples (5x10⁻⁶M). The
maxima absorption ($\lambda_{\text{abs.}}$) of the terpyridine system is not influenced by the presence of different type of substituent, no matter that the substituent is an electrono- withdrawing (-CN,-COOH) or electronodonating group (-OMe).

**Figure 31.** UV-Vis spectra of terpyridine derivatives in CH$_3$CN (5 x 10$^{-6}$ M)

Molar absorbtivity instead (log$\varepsilon$ in *Tabel 2*) is correlated with substituent’s nature. The presence of –CN group (electronowithdrawing) located on pyridine nuclei led to a slight growth of molar absorbtivity if compared with mother terpyridine 48 (with no substituent on pyridine structure). As can be deduced from *Tabel 2*, the nature of substituents located on terpyridine unit led to a slight growth of absorbance if compared with the unsubstituted derivative.
Table 2. Absorbance properties of terpyridine derivatives ($5 \times 10^{-6}$M, CH$_3$CN)

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\lambda_{\text{abs}}$(nm) ($\log{10\varepsilon}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>48</td>
<td>253 (4.84), 275 (4.88)</td>
</tr>
<tr>
<td>49</td>
<td>251 (4.86), 280 (4.57)</td>
</tr>
<tr>
<td>50</td>
<td>258 (5.17), 282 (5.08)</td>
</tr>
<tr>
<td>51</td>
<td>253 (5.07), 275 (5.14)</td>
</tr>
<tr>
<td>53</td>
<td>258 (5.02), 281 (4.93)</td>
</tr>
<tr>
<td>54</td>
<td>256 (5.09), 284 (5.09)</td>
</tr>
<tr>
<td>55</td>
<td>258 (5.12), 288 (5.14)</td>
</tr>
<tr>
<td>57</td>
<td>255 (5.07), 287 (5.11)</td>
</tr>
<tr>
<td>59</td>
<td>254 (4.77), 289 (4.86)</td>
</tr>
<tr>
<td>60</td>
<td>252 (4.84), 288 (4.85)</td>
</tr>
</tbody>
</table>

In the same conditions were recorded absorbance spectra for the same compounds using DMSO as solvent. As before, the electronwithdrawing/electronondonating influences of substituents have little contribution to the absorbance maxima peaks, which are located to a lower wavelength region (278-293 nm).

3.2.2. Fluorescence studies

Also were investigated fluorescence properties for derivatives 48-60; the solvent used was CH$_3$CN. The aim of this study was to determinate the influences of the substituents located either on pyridine or phenyl rings. In Figure 33 was noticed that electronondonating groups located on phenyl ring bring a high influence to emission intensity than electronondonating groups located on pyridine.
**Figure 33.** Emission spectra of terpyridine derivatives in CH$_3$CN (298 K)

These podands are starting materials for supramolecular assemblies such as rotaxans, coronands, cryptands, paraquats, etc.

Starting from diacid chloride 52 with diamine derivatives, were tried some macrocyclization reactions.

The reaction between 52 and 1,3-diaminopropane was carried out in ultradiluted conditions, in presence of Et$_3$N and anhydrous dichloromethane as solvent.$^{16}$ Using mass spectrometry (MALDI-TOF), were identified the monomer 77a, the dimer 77b but also the trimer derivative 77c (*Scheme 37*).

---

Scheme 37

Taking the compound 77c as example, in mass spectrum (MALDI-TOF) were observed the molecular ion peak for [M+H]+ at \( m/z = 1540.2, 1542.2, 1544.2 \) and 1546.2 (Figure 37).
A new way to achieve macrocycles which present a terpyridine unit is the synthesis of paraquats. These compounds are used in the synthesis of rotaxans and catenands, structures which can form inclusion complexes with aromatic molecules.\textsuperscript{17,18,19,20}

The synthesis of 55 with 4,4’-bipyridine (\textit{Scheme 41})\textsuperscript{21} led to formation of derivative 81 and not the desired macrocycle, the \textsuperscript{1}H NMR and \textsuperscript{31}P NMR being in concordance with this conclusion.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure37}
\caption{Mass spectrum (MALDI-TOF) fragment of compound 77c}
\end{figure}

\begin{thebibliography}{99}
\end{thebibliography}
Scheme 41

In $^1$H NMR spectrum (Figure 42) were identified the corresponding signals for terpyridine and bipyridine units. The most deshielded signals belong to pyridine protons, folowed by signals for terpyridine protons.

Figure 42. $^1$H NMR fragment spectrum for compound 81 (400 MHz, DMSO $d_6$)
PART II

Synthesis and Structural Analysis of Some New Macrocycles with Bithiophene Units
II.2. Objectives

The main target of this thesis was the synthesis of some macrocyclic compounds possessing one bithiophene unit and which contains in \( \beta \) position \(-\text{CH}_2\text{O}\) units; these units are \textit{spacers} between bithiophene unit and the ligand. For macrocyclization reactions were used tosylated polyethyleneglycol chains with different length, which are later attached to the spacers. It will be studied their supramolecular properties and also their abilities to complex cations. Due to this properties, can be obtained metallo-supramolecular structures with interesting photochemical, electrochemical catalitical and magnetical properties. More than that, the supramolecular structures would have a well-defined stereochemistry which can have a major importance when structure-property relationship is taken into consideration.

The synthetic pathway of the targeted macrocyclic derivatives is presented below in \textit{Scheme}.

\begin{center}
\includegraphics[width=\textwidth]{scheme4.png}
\end{center}

\textit{Scheme 4}

The bromination of thiophene acid \textbf{IV}, followed by esterification reaction led to derivative \textbf{III}. This compound, by homocoupling reaction ensue by reduction, forms the alcohol \textbf{II}. The diol in reaction with different ditosylated polyethyleneglycol chains, in presence of a base led to the target macrocycles \textbf{I}.
II.3. Results and discussions

The path followed to obtain the target macrocycles is shortly presented in Scheme 5. The procedure suppose the synthesis of compounds 17 and 19 in five steps; the intermediates 9-13 were obtained using procedures from literature data,\textsuperscript{22} while for the two macrocycles (17 and 19) were used modified procedures from literature.\textsuperscript{23}

\begin{center}
\includegraphics[width=\textwidth]{scheme5.png}
\end{center}

\textit{Scheme 5}


The compound 16 was used as bonding chain in macrocyclization reaction with alcohol 13. This reaction occurs in anhydrous and degassed DMF, in presence of NaH as a base, which favorise the nucleophilic attack of tosylated derivatives (Scheme 11). The ditosylated compound 16 is added dropwise at room temperature for one day, after that the reaction is left three days at room temperature.

\[
\begin{align*}
\text{OH} & \quad \text{HO} \\
\text{13} & \\
+ & \\
\text{DMF/NaH} & \text{r.t.} \\
\text{4 days} & \text{6\%} \\
\end{align*}
\]

Scheme 11

The structure of compound 17 was identified by NMR spectroscopy and mass spectrometry.

In the mass spectrum (APCI+) of 17 (Figure 8) was observed the molecular ion peak \([M+H]^+\) at \(m/z = 593.3\).
Following the same protocol as before, from alcohol 13, in reaction with ditosylated pentaethylene glycol 18, was obtained macrocycle 19, in good yields (Scheme 13).

Scheme 12

The structure of derivative 19 was identified by NMR spectroscopy and mass spectrometry. In the aromatic region of $^1$H spectrum (Figure 9) were identified two singlets for H$_{3,3'}$ (7.34 ppm) and H$_{5,5'}$ (7.25 ppm). In aliphatic area, at $\delta = 4.52$ ppm appears the singlet corresponding for –CH$_2$–O–, and in 3.54-3.60 ppm region are assigned the signals corresponding to polyethylene glycol protons.
Figure 9. $^1$H NMR fragment spectrum of compound 19
(300 MHz, acetone $d_6$)

The compounds 17 si 19 will further be tested in view of their complexation properties when added different cations (Li$^+$, Na$^+$, Ba$^{2+}$); also will be used cyclic voltammetry, UV-Vis and Fluorescence spectroscopy to inregisterate the possible modifications in their aspects when complexation occurs.
GENERAL CONCLUSIONS

In this thesis are presented the results obtained in synthesis and characterization of some new heterocyclic derivatives with terpyridine and thiophene units.

In the first part are described the methods of synthesis and structural analysis of 19 new podands with a terpyridinic unit; their structure was determined by NMR spectroscopy and mass spectrometry. Were also studied the photochemical properties by UV-Vis and fluorescence showing the differences in wavelength movement and the intensity of absorption / emission depending on the nature of solvent but also, depending on the substituents attached to the terpyridine structure.

The terpyridinic podands were used as precursors in the synthesis of new supramolecular structures; were synthesised three new macrocycles (monomer, dimer and trimer) by the reaction of acid dichloride 52 and 1,3-diaminopropane; from the reaction of terminal alchine 79 and the azide 78 (click reaction) the complex 80 was obtained and after synthesis of paraquat has been identified a new terpyridinic derivative 81. These compounds were identified and analyzed by NMR spectroscopy (¹H, ¹³C and ³¹P) and confirmed by mass spectrometry (ESI, APCI or MALDI).

In the second part are presented the results obtained in synthesis and characterisation of some new macrocycles with a bithiophene unit. Thus, we succeeded to obtain, in good yields, two new macrocycles (17 and 19), containing as “spacer” the –CH₂–O– group between the bithiophene unit and the polyethyleneglicolic chain.
The structure of these compounds was determined by nuclear magnetic resonance (NMR) and by mass spectrometry.

These compounds will be subjected to complexation reactions with various cations and neutral molecules in order to study their properties and possible applications in different fields: nanotechnology, medicine, etc.

**Keywords**: heteroarene, terpyridine, bithiophene, podands, macrocycles, absorption, fluorescence