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NEW
[2.2]PARACYCLOPHANE DERIVATIVES

Ph.D. DISSERTATION ABSTRACT

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INTRODUCTION

According to literature, cyclophane chemistry represents an important chapter in organic chemistry. The first studies on \([m,n]\)paracyclophanes were performed by Cram at the beginning of the 1950s. Cram was also the first one to use the name “paracyclophanes” for this class of bridged aromatic compounds, thus indicating their cyclic nature, as well as their two main components: the aromatic rings and the aliphatic bridges. Starting with his research, no other class or aromatic compounds has received so much attention as the cyclophanes have in the past few decades.

As far as their design goes, the versatile structure of paracyclophanes offers numerous possibilities. Thus, any aromatic system can act as an aromatic component and the aliphatic bridge can be a saturated or unsaturated polymethilenic chain. Moreover, there are even multibridged paracyclophanes as well as multi stratified paracyclophanes:

Cyclophane chemistry presents a wide interest, mainly due to their structural characteristics, like the nonplanarities of the aromatic rings and abnormal angles and bond lengths, as well as their geometrical and sterical properties, transannular properties and ring strain. Moreover, special attention is being paid to the electronic interactions between the sandwich-positioned aromatic rings, the influence that these interactions have on electrophilic aromatic substitution, as well as their role in charge transfer complex formation.

Amongst the binuclear cyclophanes, \([2,2]\)paracyclophane is the most studied molecule and it is also the molecule around which this thesis has been built. Although the number of publications in this field is impressive, this paper comes to offer more arguments in favour of continuing the research based on paracyclophane chemistry. A particular interest has been devoted to the functionalization of the aliphatic bridges, as well as the formation of new bridges, as a result of transannular interactions.
II. PERSONAL RESEARCH

Objectives

The Ph.D. Dissertation named “New [2.2]paracyclophane derivatives” aims to develop new [2.2]paracyclophane hybrid derivatives which also incorporate tetrathiafulvalene or indolizine moieties, as well as to synthesize [2.2]paracyclophanes analogous to natural endiynes.

The proposed objectives are the following:


2. Reacting the newly obtained hybrids with tetracianoquinodimethane, with the aim of obtaining complexes that display metallic properties, such as electrical conductivity.

3. The synthesis of new [2.2]paracyclophane-indolizine hybrids that are analogous to phenstatin, where the A ring is replaced by a [2.2]paracyclophane moiety.


7. The structural characterization of the newly synthesized derivatives, using elemental analysis and various spectral methods (IR, $^1$H-NMR, $^{13}$C-NMR, MS and X-ray diffraction).
II.1. [2.2]PARACYCLOPHANE SUBSTITUTED TETRATHIAFULVALENE DERIVATIVES

Because of their distinct chemical and physical properties, tetrathiafulvalene (TTF) derivatives are the subject of many studies. Considering this fact, we decided to synthesize and investigate some new [2.2]paracyclophane-TTF hybrids. In order to do this, we first obtained the 1,3-dithiolium perchlorates 5a-c, by using [2.2]paracyclophane 1 as starting material, as presented in Scheme II.1.

![Scheme II.1. The synthesis of perchlorates 5a-c](image)

Perchlorates 5a-c were then converted to 1,3-dithiol-2-thione 6 using sodium sulfide, at room temperature. By heating 1,3-dithiol-2-thione 6 with trimethylphosphite, a mixture of four TTF isomers was obtained, namely compounds 7a-d, as shown in Scheme II.2.

![Scheme II.2. The synthesis of TTF derivatives 7a-d](image)
The structures of the newly obtained compounds were established using IR, $^1$H-NMR, $^{13}$C-NMR and mass spectrometry. The structures of compounds 4a and 6 were also confirmed using X-ray diffraction.

The following stage was the reaction between the mixture of isomers and tetracyanoquinodimethane (TCNQ), which resulted in the formation of complexes that displayed metal-like properties, such as electrical conductivity. The reaction between donors 7a-d and TCNQ took place in refluxing acetonitrile and yielded four complexes, namely cis-(S$_p$, S$_p$)-TTF-TCNQ, cis-(S$_p$, R$_p$)-TTF-TCNQ, trans-(S$_p$, S$_p$)-TTF-TCNQ, trans-(S$_p$, R$_p$)-TTF-TCNQ, as a dark-green polycrystalline solid.

II.2. [2.2]PARACYCLOPHANE SUBSTITUTED INDOLIZINE DERIVATIVES

Another objective of this dissertation was the synthesis of new indolizine derivatives, analogous to phenstatin, which is known for its anti-cancer properties.$^{195}$

The first stage requires the synthesis of 4-formyl[2.2]paracyclophane 8, using [2.2]paracyclophane.$^{202, 203}$ The next step requires the addition of ethynilmagnesium chloride to the carbonyl group, when the corresponding propargylic alcohol 9 is formed. Next, the alcohol is oxidized to ketone 10 using Dess-Martin periodane (DMP).$^{204, 205}$ The final stage is a [3+2]cycloaddition between ketone 10 and various $N$-ylides generated in situ using pyridinium salts 11a-d and triethylamine. This yields the desired [2.2]paracyclophane substituted indolizines 12a-d.$^{206}$
II.3. PSEUDO-GEMINALLY SUSTITUTED PARACYCLOPHANES, ANALOGOUS TO NATURAL ENDIYNES

The aim of this chapter was to study the intramolecular electronic interactions and their influence on aromatic substitution reactions, as well as the design and synthesis of new compounds analogous to natural endiynes.

Representative to this chapter is 4,15-bisethynil[2.2]paracyclophane 20, which is synthesized according to a seven step procedure. The first reaction that was studied involved treating it with \( n \)-BuLi in anhydrous THF and then with sulfur dichloride, \( \text{SCl}_2 \). This leads to the formation of paracyclophane derivative 24, which contains a thiophenic ring, most likely formed through cycloaromatization, induced by the nucleophilic attack of a tetrahydrofurane anion on an acetylenic carbon atom in compound 23 (Scheme II.9.).

Under the same reaction conditions, paracyclophane 20 reacts with sulfur monochloride, yielding the corresponding disulfide 25 (Scheme II.10.).
Another type of studied reactions is the one involving paracyclophane 20 and a series of aliphatic and aromatic aldehydes, as shown is Scheme II.11.

**Scheme II.11.** The reaction between derivative 20 and some aliphatic and aromatic aldehydes

The reaction takes place differently when p-methoxybenzaldehyde is used. The major product is bisketone 32, most likely a product of intramolecular anionic interactions that lead to the formation of a new bridge (Scheme II.12.).

**Scheme II.12.** The reaction between paracyclophane 20 and p-methoxybenzaldehyde

Another stage in our studies involved the reaction between bis propargylic alcohol 26 and sulfur halides. To this end, paracyclophane 26 was treated with triethylamine and sulfur monochloride or sulfur dichloride, yielding the three-bridged compounds 33 and 34 (Scheme II.13.).

**Scheme II.13.** The reaction between paracyclophane 26 and SCl₂/S₂Cl₂

**II.4. REACTIONS BETWEEN PSEUDO-GEMINALLY SUBSTITUTED [2.2]PARACYCLOPHANE AND SELENIUM-BASED ELECTROPHILES**

Our investigations concerning pseudo-geminally substituted [2.2]paracyclophanes eventually led us to a series of reactions between bis acetylene 20 and some selenium electrophiles.

In order to introduce another bridge in the [2.2]paracyclophane molecule, we attempted a double addition reaction between paracyclophane 20 and one equivalent of selenium dichloride. Thus, by treating paracyclophane 20 with in situ
New [2.2]paracyclophane derivatives

generated\textsuperscript{217} selenium dichloride, in chloroform, we obtained an addition mixture of and not the expected selenium-bridged derivative (Scheme II.14.).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme14.png}
\end{center}

**Scheme II.14.** The reaction between paracyclophane 20 and \textit{SeCl}_2/\textit{SeBr}_2

Upon separation, by using spectral analysis and mass spectrometry, we were able to determine the structures of isomeric cyclic dienes 35 and 36, as well as that of the tetrachloro derivative 37. The configurations for compounds 35 (17\textit{E}, 19\textit{Z}) and 36 (17\textit{E}, 19\textit{E}) were determined using NOESY, by irradiating protons H-18 and H-20.

The reaction with selenium dibromide generated \textit{in situ}\textsuperscript{217} takes place in a similar manner, leading to two isomeric cyclic dienes, 38 and 39 and the tetrabromo derivative 40 (Schema II.14.).

Both reactions lead to the formation of elemental selenium as a byproduct. Under the same reaction conditions, but by using two equivalents of selenium dihalide, only the cyclic dienes 35, 36 and 38, 39 were formed. These results determined us to investigate the reaction between paracyclophane 20 and phenylselenyl chloride. Surprisingly, by using two equivalents of phenylselenyl chloride, only cyclic dienes 35 and 36 were formed, along with diphenyl diselenide (Scheme II.15.).

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme15.png}
\end{center}

**Scheme II.15.** The reaction between paracyclophane 20 and PhSeCl

We decided to extend these studies, by replacing 4,15-bisethynil[2.2]paracyclophane 20 with 4,15-bis(propin-1-yl)[2.2]paracyclophane 45. Thus, by reacting paracyclophane 45 with one equivalent of selenium dichloride, (17\textit{E}, 19\textit{E})-diene 46 and tetrachloro derivative 47 were obtained (Scheme II.17.).
Scheme II.17. The reaction between paracyclophane 45 and SeCl₂/SeBr₂

Similarly, by using selenium dibromide instead of selenium dichloride, (17E, 19E)-diene 48 and tetrabromo derivative 49 are obtained (Scheme II.17.).

II.5. THE BIRCH REDUCTION OF PSEUDO–GEMINALLY SUBSTITUTED [2.2]PARACYCLOPHANES

Considering the latest progress in pentalene chemistry, another direction investigated by us comprised of the reactions between some bisethynil pseudo–geminally substituted [2.2]paracyclophanes and lithium. One first such reaction is that between paracyclophane 52 and ten equivalents of lithium powder in anhydrous THF, when compound 53 is formed (Scheme II.19.).

Scheme II.19. The reaction between paracyclophane 52 and lithium

The studies were then extended to paracyclophane 45 which, under the same conditions, led to the formation of a reaction mixture, some of which could not be identified (Scheme II.20.). Upon separation using preparative TLC and analysing the different fractions obtained (spectral analysis, mass spectrometry), the structures of compounds 54, 55 and 56 were determined.

Scheme II.20. The reaction between paracyclophane 45 and lithium
CONCLUSIONS

Given the conducted research and the results obtained and presented in this paper, the following conclusions can be drawn:

1. New [2.2]paracyclophane derivatives have been synthesized and characterized by varying the substituent in position 4, with the purpose of obtaining [2.2]paracyclophane-TTF hybrids.

2. 3 New dithiocarbamates (4a-c) and 3 new 1,3-dithiolium perchlorates (5a-c) containing a [2.2]paracyclophane moiety have been obtained and their structure has been confirmed by spectral analysis and mass spectrometry. 1,3-Dithiol-2-thione 6 has been synthesized, which was then used to obtain the diastereomers 7a-d.

3. The reaction between diastereomers 7a-d and tetracyanoquinodimethane led to a mixture of four compounds. The IR spectra of this mixture displays four absorption bands that have been assigned to the CN group, at 2222 cm\(^{-1}\), 2204 cm\(^{-1}\), 2183 cm\(^{-1}\) and 2150 cm\(^{-1}\), each corresponding to a different complex.

4. Four new indolizine-[2.2]paracyclophane hybrids have been synthesized by reacting 4-(1-oxopropin-1-yl)[2.2]paracyclophane 10 with various N-ylides, generated from their corresponding piridinium salts.

5. New [2.2]paracyclophane derivatives analogous to natural endiynes have been synthesized, using 4,15-bisethynyl[2.2]paracyclophane 20 as a starting point.

6. The reactions of [2.2]paracyclophane 20 with sulfur halides have been studied. Depending on the used halide, either thiophen derivative 24 or disulfide 25 is obtained.

7. Reactions between [2.2]paracyclophane 20 and various aldehydes were also studied. The reaction with p-methoxybenzaldehyde provided unexpected results, when bisketone 32 was obtained as a major product. Its formation is likely the product of intramolecular anionic interactions and a mechanism has been proposed to explain the process.

8. The reactivity of [2.2]paracyclophane 26 was studied by treating it with sulfur chlorides (SCl\(_2\), S\(_2\)Cl\(_2\)) and the corresponding multi-bridged derivatives 33 and 34 were obtained.

9. In the case of [2.2]paracyclophane 20 and 45, interactions between the pseudo-geminally positioned groups were studied, by treatment with various selenium and selenyl halides. The reaction between [2.2]paracyclophane 20...
and one equivalent of selenium halide SeX₂ (X = Cl, Br) leads to the formation of cyclic isomeric dienes 35, 36 (X = Cl) and 38, 39 (X = Br) and the tetrahalogeno derivatives 37 (X = Cl) and 40 (X = Br). Under the same conditions, but using two equivalents of selenium halide SeX₂, only cyclic dienes 35, 36 (X = Cl) and 38, 39 (X = Br) were obtained.

10. By reacting [2.2]paracyclophane 45 with one equivalent of selenium halide SeX₂ (X = Cl, Br), cyclic dienes 46 (X = Cl) and 48 (X = Br) and tetrahalogeno derivatives 47 (X = Cl) and 49 (X = Br) were isolated. When two equivalents of selenium halide were used, only cyclic dienes 46 (X = Cl) and 48 (X = Br) were obtained.

11. The reactions between [2.2]paracyclophane 52 and [2.2]paracyclophane 45 with lithium were studied. The Birch reduction of pseudo-geminally substituted [2.2]paracyclophanes is dependent on the substituents bound to the [2.2]paracyclophane moiety. Thus, the trimethylsilyl groups lead to the formation of a new bridge with two exo-cyclic double bonds, whereas the less bulky methyl groups determined the formation of a new bridge with two endo-cyclic double bonds.

12. This Ph.D. Dissertation reports 41 new compounds.

13. Part of the results described are the subject of two scientifical papers published in ISI recognized journals and two manuscripts submitted for publication. Moreover, some of the results obtained were presented at national and international conferences.

- Published papers:


References