STEREOSELECTIVE BROMINATION OF SPIRO-1,3-DIOXANES,
SYNTHESIS AND STRUCTURAL ANALYSIS OF NEW
MACROCYCLES CONTAINING SPIRO-1,3-DIOXANES UNITS,
AS WELL AS
SYNTHESIS AND SOLVOLYSIS OF BICYCLO[1.1.0]BUT–
2-YLCARBINYL SULFONATES

Ph.D. THESIS
ABSTRACT

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1. General Introduction

The research work presented in this Ph.D. Thesis is conducted in two main fields represented one side by the study on the synthesis, stereochemistry and reactivity of some new derivatives of saturated heterocycle spiranes and on the other side by the synthesis, structural analysis and reactivity of new bicyclobutane derivatives. The first subject of the thesis was developed at “Babes-Bolyai” University Cluj-Napoca in the research group I am belonging, while the investigations concerning the second subject of my thesis were made in the research group of Prof. Manfred Christl (Universität Würzburg) during a 10 months research stage financed by a DAAD fellowship.

The research concerning the saturated six-membered ring heterocycles was oriented to the study of the stereo selective monobromination reaction of spiro compounds I and the synthesis and structural investigations of new macrocycles II incorporating spiro-1,3-dioxane units.

The objectives of the research on strained hydrocarbons were dedicated to the synthesis of new bicyclobutane derivatives III (endo and exo isomers) and to the study of their solvolysis reaction.

![Structural Formulae](image)

The bromination reaction of cyclic acetals is of high interest due to the stereoselectivity of the process and this reaction was successfully used for the enantioselective synthesis of many chiral compounds. In order to determine the itinerary of the previously reported stereo selective dibromination reaction of spiro-1,3-dioxanes it was consider of interest the aim to carry out the synthesis and structural analysis of the monobrominated precursors of these compounds.

The peculiar structural aspects of spirane compounds with six-membered rings, such the helical chirality, the anancomeric behavior and the great number of heteroatoms in
the rings, render these compounds versatile substrates in the synthesis of macrocycles with high potential for chemioselective coordination of cations and small molecules. The steric similarities of target crown ethers with similar macrocycles exhibiting special coordination properties, obtained from sugars and from heterobicycloalkanes motivate the interest for the investigations on these types of macrocycles.

The chemistry of bicyclobutane derivatives represents an interesting subject for the theoretical organic domain. Due to the important strains of the molecule, bicyclobutane derivatives exhibit peculiar transformations. It was considered of interest to carry out the synthesis of new bicyclobutane derivatives and to investigate the reactivity in the solvolysis reaction of the obtained exo and endo isomers.
Part A

2. Bromination of Monospiro-1,3-dioxanes and Access to Macrocyclic Systems

2.3. Results and Discussion

2.3.1. Stereoselective Bromination of Substituted 1,5-Dioxaspiro[5.5]-undecanes

The studies\textsuperscript{12,15,16,80} on the synthesis of dibrominated spiranes exhibiting the 1,5-dioxaspiro[5.5]undecane skeleton revealed the high regio- and diastereoselectivity of the process. The reaction performed on spiro-1,3-dioxanes \textbf{41-44, 49 and 51} under similar conditions to those used in the reaction with bromine of some 1,3-dioxolane derivatives\textsuperscript{4-7,9,10}, gave a single diastereoisomer of the 7,11-dibrominated derivatives \textbf{45-48, 50 and 52}\textsuperscript{16} (Scheme 20). NMR spectra and X-Ray investigation indicated the \textit{trans} disposal and an \textit{axial-equatorial} orientation for the bromine atoms, the two chiral carbon atoms exhibiting the same configurations (7\textit{R}11\textit{R} or 7\textit{S}11\textit{S} isomers).

It has been considered of interest, as part of this thesis, to synthesize the monobrominated precursors of these compounds, to determine their structure and to establish the mechanism and the diastereoselectivity to obtain dibrominated spiro-1,3-dioxanes.\textsuperscript{73}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{diagram.png}
\end{figure}

\begin{align*}
41 & \quad \text{R}_1 = \text{H} & 45 \\
42 & \quad \text{R}_1 = \text{CH}_3 & 46 \\
43 & \quad \text{R}_1 = \text{tC}_4\text{H}_9 & 47 \\
44 & \quad \text{R}_1 = \text{C}_6\text{H}_5 & 48
\end{align*}
New monobrominated spiro-1,3-dioxanes 53-55, 57 (Scheme 22) have been obtained by the bromination reaction (ratio spirane : bromine = 1:1) of 9, 8 or 7 substituted-1,5-dioxaspiro[5.5]undecane derivatives. The pure monobrominated compounds have been separated from the crude product (containing also dibrominated and starting spiranes) by preparative chromatographic methods or by selective crystallization.
2.3.1.1. Bromination of 9-substituted-spiro[5.5]undecane Derivative

The investigations have been carried out with compound 44 ($R_1 = C_6H_5$). Two monobrominated diastereoisomers (Scheme 22) showing the bromine atom at position 7 in equatorial (cis-53) or axial orientation (trans-53) have been identified in the crude product (ratio trans to cis = 1.8:1). The major isomer exhibits the bromine atom in axial orientation despite the positive $A$-value for the bromine atom on a cyclohexane ring ($A_{Br} = 0.48$-
The experimental ratio of isomers is close to that determined (axial:equatorial = 1.5:1) considering the calculated difference of energy between the axial and equatorial brominated isomers on the spirane system ($\Delta H^\circ = -0.91 \text{ kcal/mol}$, PC Spartan Plus program, PM3 level).

The mechanism of the reaction involves the participation of HBr as catalyst and the formation of cation I and enol ether II (Scheme 23). Further, in reaction with bromine, these cationic intermediates give the cis and trans isomers of 53. The formation of the enol ether III, involving the carbon atom, which is bearing the bromine atom, determines the equilibrium of cis and trans isomers. It was considered that the reaction proceeded under thermodynamic control and the ratio of isomers is given by the difference between their energies.

\[ \text{cis-53} \quad \text{trans-53} \]

Scheme 23

The two isomers have been separated by preparative TLC and their structure has been deduced from NMR investigations and by the molecular structure of the cis isomer established in single crystal by X-ray diffractometry. The ORTEP diagram (Figure 1) shows the chair conformation of both six-membered rings. The bond lengths, bond angles and torsion angles are in the usual range.

The NMR investigations showed the anancomeric behaviour of both rings. The axial and equatorial methyl groups at position 3 exhibit different signals for the proton as well as for the carbon atoms. The diastereotopicity of positions 2 and 4 is revealed by the $^1\text{H}$ and $^{13}\text{C}$ NMR spectra. The axial protons exhibit two doublets as the result of the geminal coupling ($J = 11.3–11.4 \text{ Hz}$) with the equatorial hydrogens. At lower fields, the
characteristic doublet of doublets for the equatorial protons with the supplementary long-range coupling ($^{4}J = 2.6$ Hz) appears.

**Figure 1.** ORTEP diagram of compound *cis*-53

### 2.3.1.2. Bromination of 8-substituted-spiro[5.5]undecane Derivative

The bromination reaction of racemic 3,3,8-trimethyl-1,5-dioxaspiro[5.5]undecane 49 (ratio spirane : bromine = 1:1) lead to the single monobrominated derivative 54 (TLC and NMR analysis) displaying the bromine atom in the opposite side of the methyl substituent of the cyclohexane ring (positions 7 and 10). The high regioselectivity of the process is correlated with a high stereoselectivity, only the *trans* isomer being obtained. The structure of this compound has been deduced from NMR investigations.

The mechanism involves the obtaining of enol ethers V and VI and of cation IV (Scheme 25). The calculations (PM3) show a higher stability (about 3.6 kcal/mol) for enol ether VI. The reaction with bromine of this enol ether can give the *cis* and *trans* isomers of 54. These isomers are in equilibrium via enol ether VII. It is considered that the reaction is proceeding under thermodynamic control and the obtaining of *trans* isomer is due to the higher stability of this compound.

The reaction of *trans*-54 with bromine led to the formation of the dibrominated spiro-1,3-dioxane 50 ($7R8R11R$ and $7S8S11S$ isomers).
2.3.1.3. Bromination of 7-substituted-spiro[5.5]undecane Derivatives

The reaction of 51 with bromine (1:1) gave the isomer of compound 55 exhibiting the methyl group in equatorial orientation. This structure of the compound has been observed both in solid state and in solution. The ORTEP diagram (Figure 4) shows the chair conformations for both rings and the measurements revealed modifications of bond angles and bond lengths at the spiro carbon atom (C-6) and at the disubstituted carbon atom of the cyclohexane ring (C-7). For example, the bonds C(6)–C(7) with 1.549 Å and C(7)–C(12) with 1.578 Å, are longer than usual.

Figure 4. ORTEP diagram of compound 55
The reaction involves the formation of oxonium ion VIII and enol ethers IX and X (Scheme 26). Despite the supposed higher stability of enol ether IX for both substituents (Me and Ph) the regio- and stereoselectivity of the processes are very different. In the reaction of compound 51, the bromine atom is connected to the tertiary carbon atom suggesting the participation in the second step of the reaction of the more stable enol ether IX. The considerably more stable conformation showing the methyl group with higher A-value (1.74 kcal/mol) in equatorial position is adopted.

Surprisingly, the reaction of 56 does not produce the benzylic brominated derivative and instead of it, the 7-bromo, 11-phenyl derivative (57) has been isolated. In this case the participation in the second step of the process of enol ether X has been taken into account. The highly stereoselective formation of trans isomer (equatorial phenyl group and axial bromine atom) is due to the high energy of cis isomer (the spirane exhibiting both bulky substituents of positions 7 and 11 in equatorial positions is strongly unstable due to the interactions of the equatorial substituent with the heterocycle).

The reaction of 55 with bromine proceeded with the obtaining of dibrominated spirane 52, whereas the reaction of 57 with bromine does not lead to the corresponding 7,11-dibrominated derivative. Moreover, all attempts to obtain the dibrominated spirane in the reaction of compound 56 with bromine (ratio 1:2), in all usual conditions (CCl₄, diethylether, CH₂Cl₂; without or with CaCO₃) failed.

Figure 5. ¹H NMR (fragment) and H,H COSY spectra of compound 55 (400 MHz, C₆D₆)
In conclusion, the structure of the monobrominated derivatives obtained in the reaction of 7-, 8- and 9-substituted-1,5-dioxaspiro[5.5]undecane with bromine (1:1) has been established by NMR investigations and by the molecular structures obtained in single crystal X-ray diffractometry. The reaction of 7- and 8-substituted spiranes proved to be of high regio- and diastereoselectivity. The further reaction of monobrominated compounds with another equiv of bromine lead to the trans isomer of 7,11-dibrominated spiro-derivatives, which proves the proposed itineraries for the bromination reaction.

2.3.2. Synthesis and Structure of Macrocycles Containing Spiro-1,3-dioxane Units

The synthesis of macrocycles of different sizes and geometries to obtain specific and selective receptors for different cations and molecules is a well-recognized topic in organic chemistry. The macrocyclisation of sugars with specific reagents (e.g. tosylated polyethyleneglycols) leads to compounds exhibiting good ability and selectivity for the coordination of various cations and molecules. Because of their chirality, macrocycles
obtained from sugars show enantioselective and enantiospecific supramolecular interactions with chiral guests and they are successfully used in enantiomers discrimination.19,81-86

The advantages of using sugars as substrates in the synthesis of macrocycles are mainly due to the chirality of the molecules and to the presence of anancomeric saturated heterocycles as part in the coordination processes. In order to obtain different crown ethers with similar properties the synthesis of macrocycles exhibiting chiral spiro20,21,87,88 or bicyclo89-94 units with saturated six membered ring heterocycles was recently developed. The NMR and Electro spray mass spectrometry studies on coronands and cryptands with spiro units revealed the high coordination capacity of these macrocycles and the chemio- and enantioselectivity of this process.20,87

In this context of interest related to the crown-like structure, the synthesis and the structure of some macrocycles containing the tetraoxaspiro[5.5]undecane skeleton was studied.103 The main feature of these substrates is the facility to prepare them in good yields and using accessible reagents. Spiro-1,3-dioxanes 62 bearing aromatic groups with an appropriate functionality in the acetal part of the heterocycles were easily prepared by the acetalisation reaction of aromatic aldehydes 60 with pentaerythritol 61 (Scheme 29).95-97

![Scheme 29](image)

3,9-Diaryl-2,4,8,10-tetraoxaspiro[5.5]undecane derivatives are chiral and they exhibit the characteristic axial and helical chirality of spiro compounds with six-membered rings.23,24,98-100 These compounds display at the same time three chiral elements: a helix with $M$ or $P$ configuration (characteristic for polyspiranic skeletons with six-membered rings), and two chiral axes (Figure 8), C(3)–C(6) with the substituents Ar and H at C-3, cycle B and an absent ligand at C-6 and C(6)–C(9) with the substituents Ar and H at C-9, cycle A and an absent ligand at C-6, exhibiting $aR$ or $aS$ configurations. Theoretically, eight stereoisomers are possible.
On the other hand the 1,3-dioxane rings are anancomeric, the high A-value of aryl groups located at the acetal part of the 1,3-dioxane ring \( (e.g. \ A_{Ph} = 13.04 \ \text{kJ/mol}) \) determines the strong shifting of the conformational equilibria involving the flipping of the 1,3-dioxane rings towards only two conformers with both aryl groups in equatorial orientation.\(^{76,101,102}\) Owing to the chirality of the spiro skeleton, these compounds show separable enantiomers and are obtained under the usual conditions of the acetalization reaction as racemic mixtures (\( P \) and \( M \) configurations of the helix, Scheme 30).\(^{16}\)

### 2.3.2.1. Synthesis of the Macrocycles

Spiro-1,3-dioxane 62a (Ar = \( m \)-C\(_6\)H\(_4\)-OH) in reaction with ditosylated 64a-f (method A) and dibrominated 65a-f (method B) (poly)ethylene glycol(s) in 2-propanol, using high-dilution conditions was transformed in good yields up to 61% into the corresponding macrocycle derivatives 66-71 (Scheme 32, Table 10).
Except for the commercially available ditosylated 64e and dibrominated 65a-c, the starting materials used in the macrocyclization reactions were also synthesized. Spiro-1,3-dioxane 62a was prepared in good yield (60%) by the acetalization reaction of m-hydroxibenzaldehyde and pentaerythritol using the method described in the literature for this compound.97

The cyclization reactions led to the formation of monomeric (68a-71a, m = 1) and dimeric (66b-71b, m = 2) macrocycles. Monomers and dimers were separated by flash chromatography. In some fractions collected in the separation of 66, 67 and 68, the FAB and MALDI\(^{+}\) spectra show also the presence of small amounts of trimeric macrocycles.

The ratio of monomers to dimers is mainly correlated with the lengths of the polyethoxylated chains (Table 10). If the chain is short (one or two ethyleneoxy units, n =
only the dimers are obtained (66b and 67b), but when the chain is long enough (n = 4, 5, 6) the monomers are the major product and the ratio monomer / dimer (a:b) varies from 1.5 to 2.1. The highest preference for the formation of monomer is observed in the synthesis of 71. The ratio of monomeric to dimeric macrocycles is somewhat higher in the reactions with ditosylated polyethyleneglycols (A). In the synthesis of 68, both monomer and dimer are formed, but in this case the dimer is the major product [ratio monomer / dimer = 0.1 (A) and 0.5 (B)].

Yields in the reactions with ditosylated polyethyleneglycols are higher (28–61%) than in the reaction with the dibrominated derivatives of polyethyleneglycols (5–45%). These differences are smaller when the polyethoxylated chains are long enough (n = 4–6) and increase dramatically with the shortness of the chains (Table 10).

Table 10: Results (yields in separated compounds, %) in the synthesis of compounds 66-71 (methods A and B)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Method A</th>
<th>Method B</th>
<th>Ratio a:b</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>monomer</td>
<td>dimer</td>
<td>Global</td>
</tr>
<tr>
<td>66</td>
<td>-</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>67</td>
<td>-</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
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<td>37</td>
</tr>
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<td>19</td>
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</tr>
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<td>32</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>71</td>
<td>41</td>
<td>20</td>
<td>61</td>
</tr>
</tbody>
</table>

Owing to the chirality of the spiro skeleton, monomers are obtained as racemates and dimers are obtained as mixtures of like (the spiro units have the same configurations of the helix: PP, MM) and unlike (the spiro units have different configurations of the helix: MP) isomers. Only the like isomer of 71b could be separated by flash-chromatography as single compound.
2.3.2.2. Solid State Molecular Structures

The molecular structure in solid state was determined for monomers 69a, 71a and the dimer 69b (Figures 9-11). In all the investigated structures, the 1,3-dioxane rings exhibit chair conformations and the bond lengths and bond angles show normal values in the case of compounds 69a and 69b (the length between the substituted carbon of the spirane fragment and the carbon of the phenyl is longer than usual, possible due to the proximity with the opposite spirane unit), as well as for compound 71a (which crystallised including a molecule of water).

In 69a (Figure 9), the dihedral angles between the best planes of each heterocycle (the plane formed by the exocyclic bonds of the acetal carbon atom) and the plane of the corresponding aromatic ring exhibit values close to 90° (C⁷C⁶C¹ⁱ / C¹²C¹⁳C¹⁴C¹⁵C¹⁶C¹⁷ = 85.9° and C¹C⁶C⁵ / C¹⁸C¹⁹C²⁰C²¹C²²C²³ = 83.7°), which demonstrate the orthogonal orientation of the aromatic substituents. The equatorial aromatic ring in the majority of the investigated molecular structures of 2-aryl-1,3-dioxanes displays a bisectional orientation (the values of the reference dihedral angles are close to 0°).³⁶

![Figure 9](image)

**Figure 9** ORTEP diagram of compound 69a

The molecular structure of 71a reveals the crystallization of the compound with the inclusion of a molecule of water. The water forms hydrogen bonds with the oxygen atom O₃₃ of the chain (measured O₃₃- - - H distance d = 1.906 Å). The IR spectrum of the moist
compound confirmed the presence of the water and exhibits two distinct O-H stretch bands at 3498 cm\(^{-1}\) and 3598 cm\(^{-1}\).

The structure of 71a (Figure 10) revealed a peculiar orientation of the aromatic substituents. The reference dihedral angles between the best planes of each heterocycle and the plane of the corresponding aromatic ring exhibit values (C\(^{20}\)C\(^{21}\)C\(^{22}\) / C\(^{26}\)C\(^{27}\)C\(^{28}\)C\(^{29}\)C\(^{30}\)C\(^{31}\) = 48.8\(^{\circ}\) and C\(^{23}\)C\(^{21}\)C\(^{25}\) / C\(^{13}\)C\(^{14}\)C\(^{15}\)C\(^{16}\)C\(^{17}\)C\(^{18}\) = 59.6\(^{\circ}\)) close to the average of the characteristic values for bisectional (0\(^{\circ}\)) and orthogonal (90\(^{\circ}\)) orientations.

The investigated crystal of 69b (selected form a mixture of isomers) (Figure 11) contains a centrosymmetric molecule (group P 21/c) and represents the unlike isomer. The aromatic substituents exhibit modified orientations from the trivial bisectional rotamer. Two of the rings exhibit orthogonal disposition (C\(^7\)C\(^6\)C\(^{11}\) / C\(^{12}\)C\(^{13}\)C\(^{14}\)C\(^{15}\)C\(^{16}\)C\(^{17}\) = C\(^7\)A\(^{6}\)A\(^{11}\)A / C\(^{12}\)A\(^{13}\)A\(^{14}\)A\(^{15}\)A\(^{16}\)A\(^{17}\) = 86.9\(^{\circ}\)), while the other two rings exhibit a peculiar orientation (C\(^1\)C\(^6\)C\(^5\) / C\(^{18}\)C\(^{19}\)C\(^{20}\)C\(^{21}\)C\(^{22}\)C\(^{23}\) = C\(^1\)A\(^{6}\)A\(^{5}\)A / C\(^{18}\)A\(^{19}\)A\(^{20}\)A\(^{21}\)A\(^{22}\)A\(^{23}\) = 40\(^{\circ}\)) intermediate between orthogonal and bisectional rotamers. The macrocycle exhibits a structure in which two of the aromatic rings (C\(^{18}\)C\(^{19}\)C\(^{20}\)C\(^{21}\)C\(^{22}\)C\(^{23}\) and C\(^{18}\)A\(^{19}\)A\(^{20}\)A\(^{21}\)A\(^{22}\)A\(^{23}\)) are relatively close in space (d = 9.58 Å) and show a parallel orientation (the measured value of the angle between the planes of the two rings is 0.0\(^{\circ}\)). The peculiar shape of the structure of 69b, showing the collapse in the middle part of the
macrocycle, suggests that this compound may be able to coordinate as a ditopic “host” molecule. Generally the reported di- and polytopic “host” molecules exhibit two or more distinct cavities\textsuperscript{112-119}, but interesting macrocycles in which two cations are coordinated by the same cycle were also reported\textsuperscript{120-122}. The low resolution of 69b (R = 0.159) is due on the one hand to the poor quality of the crystal and on the other hand to modifications (in the crystal) of the positions of the atoms of the chain even at low temperature (120 K).

![Figure 11](tep_diagram.png) TEP diagram of compound 69b

2.3.2.3. Structural Aspects in Solution

The structure of the compounds in solution was investigated by high-field NMR spectroscopy (600 MHz). The NMR spectra of the monomer and of the dimer of the same term are similar. The two isomers of the dimer, like and unlike, exhibit overlapped signals and could not be discriminated.

The anancomeric behaviour of the spiro skeleton leads to the recording of different signals for protons in the equatorial and axial positions. The chirality of the molecule induces the diastereotopicity of the CH\textsubscript{2} groups of the same six-membered ring heterocycle. One of these groups lies over the other 1,3-dioxane ring of the spirane (methylene “inside” group; positions 5 and 7, Scheme 30) and the signals of these protons (especially the equatorial ones) are strongly deshielded, with chemical shifts $\delta = 4.82$–4.93 ppm (Table 15). The other CH\textsubscript{2} group is orientated in the opposite direction (methylene “outside”
group; positions 1 and 11, Scheme 30) and the methylenic protons exhibit usual δ values (3.27–3.83 ppm).\textsuperscript{12,130-131} Remarkably is the diastereotopicity recorded for the equatorial protons (Table 15) and unusual values up to 1.5 ppm were observed, while for the axial diastereotopic protons this difference is considerably lower (values up to 0.45 ppm).

The signals of the protons belonging to the chains are relatively simple for the first terms of the series (66-67), but the spectra of higher terms (68-71) exhibit well-separated signals only for the more deshielded protons of the ethyleneoxy groups directly connected to the aromatic rings. The other protons of the chain show overlapped signals.

Table 15.\textsuperscript{14} NMR data (spirane CH\textsubscript{2} groups) for compounds 66b-71b and 68a-71a (600 MHz, C\textsubscript{6}D\textsubscript{6} or CDCl\textsubscript{3}*)

<table>
<thead>
<tr>
<th>Compound</th>
<th>CH\textsubscript{2}-in</th>
<th>CH\textsubscript{2}-out</th>
<th>CH\textsubscript{2}-112</th>
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</tr>
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<td>70.97</td>
<td>70.22</td>
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<td>70.76</td>
<td>0.47</td>
</tr>
<tr>
<td>71b (like)</td>
<td>71.58</td>
<td>70.87</td>
<td>0.71</td>
</tr>
</tbody>
</table>

* Compounds insoluble in C\textsubscript{6}D\textsubscript{6};

Because of the similarity of the compounds 66-71, a detailed presentation of the NMR spectra will be further made only for one term of the monomers and dimers series, respectively. The assignments of the signals were based on two-dimensional NMR spectra.
The dimer 67b (Figure 12) exhibit separated signals for each type of proton (Figure 13) and carbon atoms.

The aromatic protons show four distinct peaks in the region 6.96–7.57 ppm of the $^1$H NMR spectrum. Based on H,H COSY (Figure 14a) and NOESY (Figure 15) spectra, the most deshielded signal, a broad singlet at 7.57 ppm was assigned to the equivalent protons at position 49, 54, 55, 60. At higher fields appears a doublet (7.31 ppm) for hydrogen atoms at position 12, 22, 36, 46 and then a false triplet (from overlapped doublet of doublets) for the protons at positions 11, 23, 35, 47. To protons at positions 10, 24, 34, 48 was assigned the doublet of doublets at 6.96 ppm, which is confirmed by the interactions detected in the NOESY spectrum, with the axial protons at position 14, 20, 38, 44. Also, the observed interactions in the NOESY spectrum between 49-H and the axial proton at position 14 (5.19 ppm), as well as with the methylene group 7-CH$_2$ (3.89 ppm) from the aliphatic chain, sustained these assignments.

The methylene protons give two different false triplets (from an AA’BB’ system), one at 3.89 ppm for the groups nearer from the phenyl and the other one at higher field, 3.57 ppm, for the 4-, 6-, 28- and 30-CH$_2$.

The singlet at 5.31 ppm belongs to the axial protons attached at the carbon atoms bearing the phenyl groups, and interactions in the NOESY spectrum (Figure 15) with the axial dioxane protons can be observed. The H,H COSY (Figure 14b) as well as the NOESY spectra were very useful in the assignment of the dioxane proton. It was possible to establish the axial-equatorial pairs of each position. The methylene “inside” group exhibit a
doublet of doublets at 5.02 ppm for the equatorial disposition and a doublet at 3.53 ppm for the axials, while the “outside” group present a doublet of doublets at 3.42 ppm for equatorial protons and the corresponding doublet for the axial protons at 3.07 ppm.

Figure 13. $^1$H NMR spectrum of compound 67b (600 MHz, C$_6$D$_6$)

Figure 14. Fragments from H,H COSY spectrum of compound 67b
Figure 15. NOESY spectrum of compound 67b

The structure of the new macrocycles was also investigated by mass spectrometry, using the FAB (Fast Atom Bombardment) and MALDI (Matrix Assisted Laser Desorption Ionization) method, which are the appropriate techniques for the macromolecules with a large molecular mass\(^{132}\) (e.g. from 458.51 for 68a to 1181.34 for the highest term, 71b).

Except for the protonated form of the molecular ion \((M + H)^+\), the presence of some metal complexes could be detected for each compound (Table 16).
Table 16. FAB-MS and MALDI data of compounds 66-71

<table>
<thead>
<tr>
<th>Compd. (M)</th>
<th>Technique</th>
<th>(M+H&lt;sup&gt;+&lt;/sup&gt;)</th>
<th>(M+Na&lt;sup&gt;+&lt;/sup&gt;)</th>
<th>(M+K&lt;sup&gt;+&lt;/sup&gt;)</th>
<th>(M+Na&lt;sup&gt;+&lt;/sup&gt;+K&lt;sup&gt;+&lt;/sup&gt;)</th>
<th>(M+Cs&lt;sup&gt;+&lt;/sup&gt;)</th>
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<tbody>
<tr>
<td>66b (740.80)</td>
<td>FAB-MS</td>
<td>741.0</td>
<td>-</td>
<td>-</td>
<td>801.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MALDI</td>
<td>-</td>
<td>762.9</td>
<td>779.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>67b (828.91)</td>
<td>FAB-MS</td>
<td>829.2</td>
<td>-</td>
<td>-</td>
<td>889.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MALDI</td>
<td>829.4</td>
<td>851.3</td>
<td>867.4</td>
<td>888.5</td>
<td>961.4</td>
</tr>
<tr>
<td>68a (458.51)</td>
<td>FAB-MS</td>
<td>460.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MALDI</td>
<td>459.1</td>
<td>481.0</td>
<td>497.0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>68b (917.01)</td>
<td>FAB-MS</td>
<td>917.1</td>
<td>940.7</td>
<td>-</td>
<td>978.0</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MALDI</td>
<td>917.6</td>
<td>939.7</td>
<td>-</td>
<td>1052.0</td>
<td>-</td>
</tr>
<tr>
<td>69a (502.56)</td>
<td>FAB-MS</td>
<td>503.0</td>
<td>524.0</td>
<td>-</td>
<td>-</td>
<td>638.0</td>
</tr>
<tr>
<td>69b (1005.12)</td>
<td>FAB-MS</td>
<td>1006.0</td>
<td>1027.9</td>
<td>1034.9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>70a (546.61)</td>
<td>FAB-MS</td>
<td>547.0</td>
<td>569.0</td>
<td>584.0</td>
<td>-</td>
<td>682.0</td>
</tr>
<tr>
<td>70b (1093.23)</td>
<td>FAB-MS</td>
<td>1093.0</td>
<td>1115.0</td>
<td>1131.0</td>
<td>1153.8</td>
<td>-</td>
</tr>
<tr>
<td>71a* (608.68)</td>
<td>FAB-MS</td>
<td>609.0</td>
<td>613.0</td>
<td>-</td>
<td>-</td>
<td>726.0</td>
</tr>
<tr>
<td>71b (1181.34)</td>
<td>FAB-MS</td>
<td>1180.6</td>
<td>1202.2</td>
<td>1218.0</td>
<td>1239.6</td>
<td>-</td>
</tr>
</tbody>
</table>

The molecular mass include one molecule of water; FAB-MS, 591.0 (M<sup>+</sup>-H<sub>2</sub>O)

The complexation could occur by the workup of the reaction mixture or even by the preparation of the sample (when ppm amounts of the sodium existing in the glassware may be extracted by the investigated compound). The frequently observed complexes with sodium and with potassium - and for some dimers even the peak (M+Na<sup>+</sup>+K<sup>+</sup>) was recorded - demonstrates the characteristic high affinity of these crown-like systems for the alkali metals and the possibility to coordinate as a ditopic “host” molecule<sup>120,121,122</sup> (Figure 23). For some compounds, a peak corresponding to a cesium complex was also identified (Table 16).

An experimental study concerning the ion selective electrodes for potentiometric determination of potassium revealed stability and a very good reproducibility for the monomer 70a and for the dimer 69b.<sup>133</sup> Compound 70a was incorporated into a polyvinyl chloride matrix membrane and then used for the construction and analytical evaluation of a K ion selective electrode. The linear response range of the electrode was between 10<sup>-1</sup>–10<sup>-4</sup> M for classical electrodes and 10<sup>-2</sup>–10<sup>-6</sup> M for nanoelectrodes. The
membrane selectivity for classical electrodes was studied in the presence of the interfering ions such Li$^+$, Na$^+$ and NH$_4^+$. Under special circumstances, it was observed that the electrode has also a linear response (10$^{-3}$–10$^{-1}$ M) for NH$_4^+$. 

![Diagram](image)

68a-71a  n = 1-3
M = Na, K

66b-71b  n = 1-6
M = Na, K

Figure 23

The identification of the possible other cation complexes which give the peaks in mass spectra as well as the selectivity of this process requires still more investigation (i.e. using Electrospray techniques).

In conclusion, the synthesis of a systematic series of monomer and dimer macrocycles including spiro-1,3-dioxane units was carried out in good yields by the high-dilution method. The solid state molecular structures revealed peculiar positions of the aromatic rings. The structure of 71a showed the coordination of one molecule of water and the important interactions of this molecule with the oxygen atoms of the macrocycle. The NMR spectra revealed the anancomeric structure of the spiranic skeleton and the significant differences of magnetic environment for some homomorphic groups as a result of the chirality of the spiro skeleton and of the magnetic anisotropy of the aromatic rings. The mass spectroscopy investigation indicated the affinity for alkali metals as sodium, potassium or cesium.
Part B

3. Synthesis and Solvolysis of Bicyclo[1.1.0]but-2-ylcarbinyl Sulfonates

3.2. Results and Discussion

In detailed investigations, Bentley, Christl et al.\textsuperscript{77-80} have studied the influence of the bicyclo[1.1.0]butane system on the rate of the heterolytic dissociation of bicyclo[1.1.0]butyl-2-carbinyl esters. The present work is an extension of that research and deals with the synthesis of \textit{endo}- and \textit{exo}-bicyclo[1.1.0]but-2-ylcarbinol as well as preparation and solvolysis of their sulfonates.

3.2.1. Synthesis of the Bicyclo[1.1.0]butane-2-methanols and Their Reaction with Sulfonic Acid Chlorides

Recently,\textsuperscript{80} synthesis, structure, and solvolysis of \textit{endo},\textit{endo}- (\textit{endo},\textit{endo}-\textit{9}) and \textit{exo},\textit{exo}-bicyclo[1.1.0]butane-2,4-dimethanol dimesylate (\textit{exo},\textit{exo}-\textit{9}) were reported. The solvolyses of the two isomers took an entirely different course as demonstrated by the different products. This results, together with the kinetic data, questioned a report by Breslow et al.\textsuperscript{81} on solvolyses of the dimethylbicyclo[1.1.0]but-2-ylcarbinyl tosylates \textit{endo}- and \textit{exo}-\textit{10}.

![Diagram of bicyclo[1.1.0]butane-2-methanols and their reaction with sulfonic acid chlorides]

**Figure 3**

3.2.1.1. Synthesis of the Bicyclo[1.1.0]butane-2-methanols

In this context, it was of interest to study the solvolysis of \textit{endo}- and \textit{exo}-bicyclo[1.1.0]but-2-ylcarbinyl sulfonates, in which the methyl groups at the bicyclobutane bridgehead positions of \textit{endo}- and \textit{exo}-\textit{10} are replaced by hydrogen atoms.
The bicyclo[1.1.0]butane-2-methanol skeleton was obtained in three steps from 1,3-butadiene via dibromocyclopropanation and epoxidation, followed by bromine-lithium exchange with 1-butyllithium and the intramolecular nucleophilic attack of the carbenoid at the epoxide group.

The addition of one equivalent of dibromocarbene to the 1,3-butadiene (17) was selectively achieved and gave 1,1-dibromo-2-vinylcyclopropane (18) in 74% yield, which is similar to yields described in the literature.\textsuperscript{85,86} Dibromocarbene was generated from potassium tert-butoxide and bromoform in anhydrous pentane at –10 °C (Scheme 27).

![Scheme 27](image)

Epoxidation of the remaining double bond was carried out with dimethylidioxirane in acetone (Scheme 28). Excellent yields are the most significant advantage of the dioxirane method.\textsuperscript{87,88} Two other methods were also tried for the syntheses of erythro- and threo-19, namely the oxidation of 18 with m-chloroperbenzoic acid (MCPBA) and the reaction of 18 with N-bromosuccinimide/H\textsubscript{2}O followed by treatment of the bromohydrines with concentrated NaOH. The first method gave a very low yield (11–15%) for the two diastereoisomers (ratio 1:1) and many byproducts. In the second case, a better yield was obtained (30–35%), but the ratio erythro: threo was 0.3:1

![Scheme 28](image)
After addition of a solution of dimethylidioxirane in acetone at 0 °C to 1,1-dibromo-2-vinylecyclopropane, the mixture was stirred at room temperature for one day. The removal of the acetone gave the epoxides 19 in 75 % yield. The NMR spectrum of the crude product reveals the presence of a quite pure diastereomeric mixture of threo-19 and erythро-19 in the ratio of 1:1. The separation of the two isomers was achieved by flash chromatography on silicagel with 5% tert-butyl methyl ether in light petroleum ether (b.p. 30–50 °C) as eluant.

The identification of the compounds 19 is based on routine $^1$H- and $^{13}$C-NMR spectra together with the two-dimensional H,H-COSY, C,H-COSY, and NOESY spectra. Only one reference to compounds of this type was found in the literature, namely a the paper of Mannafov et al. from 2001, who had obtained two isomers analogous to 19 as a mixture after addition of dichlorocarbene to vinyloxirane in a total yield of about 39%. After the isolation of the products by fractional distillation, the authors determined the structure exclusively by $^1$H- and $^{13}$C-NMR spectra. However, the configurational assignments made by them have to be reversed on the basis of the present results.

The decisive criterion for the specific assignment of the spectra to threo-19 and erythро-19 was provided by the transformation to the bicyclobutanemethanols endo-20 (Scheme 29) and exo-20 (Scheme 30), respectively.

These reactions were carried out at −75 °C under nitrogen by addition of 2.2 equivalents of 1-butyllithium to a solution of one of the epoxides in anhydrous diethyl ether. They were highly diastereoselective and diastereospecific, as threo-19 gave

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* I thank Prof. W. Adam and Mr. J. Bialas for supplying this reagent.
exclusively endo-20 (Scheme 31) and erythro-19 exclusively exo-20 (Scheme 32). The clean separation of the two epoxides proved to be very important, because the separation of mixtures of the very sensitive bicyclobutanemethanols 20 would have been extremely difficult if not impossible. Obtained in yields of ca. 30%, both isomers were contaminated with some 1-butanol as the major impurity.

Scheme 30

Obviously, these reactions proceed in complete analogy to the synthesis of tricyclo[4.1.0.0^{2,7}]heptan-3-ol (16) by Szeimies and Tischer.\textsuperscript{82} Accordingly, at first, the bromine atom located cis to the oxirane subunit in 19 is exchanged by a lithium atom, as illustrated in Schemes 31 and 32. Then the carbenoid attacks the proximate oxirane carbon atom intramolecularly in an Sn2-type reaction. The stereochemical requirement of an attack from the rear with respect to the leaving group, the oxygen atom, is the key for the specific formation of endo- and exo-20 from threo- and erythro-19, respectively. The alcoholates of the 1-bromine derivatives of endo- and exo-20 are the products of these processes. Then, the second equivalent of 1-butyllithium exchanges the remaining bromine atom in the alcoholates and, finally, the target alcohols are the result of the hydrolysis.

The purification of the crude alcohols was performed by a slow evaporation at room temperature under reduced pressure and condensation of several fractions in cold receivers. This procedure allowed the separation from 1-bromobutane and from the major quantity of 1-butanol, an almost unavoidable by product of reactions of 1-butyllithium.
The structure of the new compounds was proved by $^1$H-, $^{13}$C-, C,H-COSY, and C,H-coupled NMR spectra, but also by mass spectrometry including high resolution mass spectrometry.
A characteristic feature of \textit{endo-20} is its $C_5$ symmetry, giving rise to four one-proton and two two-proton signals. The methylene group causes as a doublet of doublets due to the coupling with the OH group ($J = 5.9$ Hz) and with the proton in position 2 ($J = 7.2$ Hz), (figure 10). The latter exhibits a signal as complicated as a triplet of quartets of doublets. The triplet originates from the coupling with the methylene group, whereas the quartet results from equal magnitudes (3.3 Hz) of the coupling constants to the
bridgehead protons (1-H, 3-H) and 4-H_α. By the _exo_ orientation of 2-H and 4-H_α, the bonds between these protons form a double W pathway (Figure 9), which is why their mutual coupling is relatively large, although it is transmitted by four bonds. The doublet is due to the weak coupling (0.6 Hz) with 4-H_β.

The decisive information that proved the formation of the bicyclobutane skeleton is the signal at 1.7 ppm, which shows a one-bond coupling constant of 201.3 Hz in the proton-coupled $^{13}$C-NMR spectrum (Figure 11). This high value is characteristic for the bridgehead carbon atoms, since the corresponding carbon atom orbital is approximately an $sp^{1.5}$ hybrid. As mentioned above, the $s$ character is linearly correlated with the one-bond coupling constant. The supplementary splitting of the signal into a sextet of $J = 3.5$ Hz is due to couplings with 2-H, 3-H (or 1-H), 4-H_α, and 2-CH_2.

Figure 11. Detail from C,H-coupled NMR spectrum of _endo-20_ (101 MHz, C_6D_6)

3.2.1.2. Synthesis of the Bicyclo[1.1.0]but-2-ylcarbinyl Sulfonates

Since the alcohols _20_ could not be obtained in the pure state, the preparation of their _p_-nitrobenzoic acid esters was tried (Scheme 33) by the use of a literature method. To a solution of _endo-20_ or _exo-20_ in anhydrous pyridine, a slight excess of _p_-nitrobenzoyl chloride was added at 0 °C. The workup of the reaction after 30 minutes
and the chromatographic purification of the crude product provided the expected $p$-nitrobenzoate (21) only in the case of $endo$-$\text{20}$. The recrystallisation from hexane in a Craig tube gave colourless crystals with m.p. 41-44 °C.

\[
\text{PNB} = 4\text{-NO}_2\text{-C}_6\text{H}_4\text{-COCl}
\]

\[
\begin{align*}
\text{H} & \quad \text{CH}_2\text{OH} & \quad \text{end} & \quad \text{20} \\
\text{H} & \quad \text{CH}_2\text{OPNB} & \quad \text{21} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{CH}_2\text{OH} & \quad \text{end} & \quad \text{20} \\
\text{H} & \quad \text{CH}_2\text{OPNB} & \quad \text{22} \\
\end{align*}
\]

\[
\begin{align*}
\text{HO} & \quad \text{CH}_2\text{OPNB} & \quad \text{23} \\
\end{align*}
\]

\begin{center}
Scheme 33
\end{center}

Since the purpose of this project was the synthesis of sulfonates of the alcohols 20 for their subsequent solvolysis, the experiments to prepare mesylates were the next steps (Scheme 34).

\[
\begin{align*}
\text{H} & \quad \text{CH}_2\text{OH} & \quad \text{end} & \quad \text{20} \\
\text{H} & \quad \text{CH}_2\text{OMs} & \quad \text{24} \\
\end{align*}
\]

\[
\begin{align*}
\text{H} & \quad \text{CH}_2\text{OH} & \quad \text{exo} & \quad \text{20} \\
\text{H} & \quad \text{CH}_2\text{OMs} & \quad \text{25} \\
\end{align*}
\]

\begin{center}
Scheme 34
\end{center}
The reaction of *endo*-20 with methanesulfonyl chloride in the presence of triethylamine at –35 °C was carried out in CDCl$_3$ and NMR spectra were recorded at –30 °C without workup of the reaction mixture. The progress of the reaction was monitored by TLC on basic Al$_2$O$_3$. The repetition of the measurements at 0 and 27 °C after a few hours did not indicate significant changes. However, after one day at room temperature, ca. one third of the amount of 24 had been converted into pent-3-en-1-yl mesylate (26) and another pent-3-en-1-yl species in the ratio of 2:1 (Scheme 35). The other pent-3-en-1-yl species could be the ether 27, which is expected to be formed by reaction of 24 with a trace of water. After nine day, at room temperature, the conversion of 24 was complete.

The preparation of the mesylate 25 by treating *exo*-20 as *endo*-20 failed (Scheme 34). Most probably, triethylammonium chloride, the necessary byproduct of the mesylation reaction, is a strong enough acid to destroy *exo*-22 in an acid-catalysed process.

In view of the high sensitivity of *exo*-20 even towards rather weak acids, the synthesis of the tosylate 28 by a procedure that avoids acids entirely was taken into consideration. Such a reaction was applied for the preparation of the tosylate of *endo,endo*-bicyclo[1.1.0]butane-2,4-dimethanol with a satisfying result in 1978. Accordingly, *exo*-20 was converted into its alcoholate by sodium hydride in anhydrous THF (Scheme 36). A solution of *p*-toluenesulfonyl chloride in anhydrous THF was then added at –17 °C. Workup of the reaction mixture provided a colourless oil, which was shown by NMR spectroscopy to be an essentially pure mixture of 28 and 1-butyl tosylate, with the latter having been formed from 1-butanol that had contaminated *exo*-20. The structure of 28 was secured by the use of $^1$H-, $^{13}$C-, and C,H-coupled NMR spectra, as well as H,H- and C,H-COSY spectra.
3.2.2. Solvolysis of Bicyclo[1.1.0]but-2-ylcarbinyl Sulfonates

3.2.2.1. Solvolyses of the endo-Bicyclo[1.1.0]but-2-ylcarbinyl Mesylate

Product studies of solvolysis of mesylate 24 were performed in two solvents:

a) 75% v/v acetone/water and

b) [D₄]methanol/NaOCD₃ (deuterated sodium methoxide).

On treatment of 24 with aqueous acetone containing triethylamine at room temperature over 18 hours, pent-3-en-1-yl mesylate (26) and 3-pentenol (43) (Scheme 42) in the ratio of 2:1 were formed. Present as an impurity of 24, 1-butyl mesylate did not undergo a reaction under these conditions.

The second solvolysis of 24 was performed in deuterated methanol in the presence of deuterated sodium methoxide and monitored by NMR spectroscopy. The products were [D₃]methylpent-3-en-1-yl ether (44) and pent-3-en-1-yl mesylate (26) (Scheme 44). The ratio of 26:44 was 1:2 at the beginning, 1:4 after two hours, and 1:7 after 8.5 hours. The ratio of 24:(26+44) was 6:1 at the beginning, 1:3 after two hours, and after 8.5 hours, 24 had been completely consumed. 1-Butyl mesylate was converted into 1-butyl [D₃]methyl ether to about 40% within 8.5 hours.
In both solvolyses, only rearranged products were formed, which have a structure that is analogous to compound 33, the product of the hydrolysis of \textit{endo}-\textit{10}$^{81}$, and to compounds 34 and 35, the products of the solvolyses of \textit{endo,endo}-\textit{9}$^{80}$. As shown in Scheme 45, the dissociation of 24 should be accompanied by a Wagner-Meerwein rearrangement, giving rise to the nonclassical cation 45, which is attacked by the nucleophils present in the reaction mixtures to bring about ring-expanded products such as 26, 43, and 44.

3.2.2.2. Solvolyses of the \textit{exo}-Bicyclo[1.1.0]but-2-ylcarbinyl Tosylate

The first experiments toward a solvolysis of the tosylate 28 were carried out in mixtures of water and acetone and seemed to proceed with an unexpectedly low reaction rate. In addition, a product could not be identified. These problems were solved by running a methanolysis as in the case of mesylate 24. Accordingly, 28 was dissolved in D$_3$COD/NaOCD$_3$ and the progress of the reaction was monitored by NMR spectroscopy (Scheme 46). The formation of \textit{exo}-bicyclo[1.1.0]butane-2-yl [D$_3$]methyl ether (46) was observed with almost quantitative yield. Present as an impurity as mentioned above, 1-butyl mesylate was converted into 1-butyl [D$_3$]methyl ether with virtually the same rate.
Considering the high probability of an $S_N2$ reaction, a second experiment was performed, in which the concentrations of the $exo$-tosylate $28$, 1-butyl tosylate and $D_3$CONa were only half of those of the previous experiment, in comparison to which the reaction rates were reduced to about half the value. Qualitatively, this is in line with the anticipation on the basis of an $S_N2$ reaction, although the rate equation demands a reduction to one forth, if the concentrations of the substrates (tosylates and NaOCD$_3$) have only half the value of their previous magnitudes.

Since a solvolysis product of compound $28$ should be observed under conditions of the conductometric rate measurements, another two experiments were performed.

For an efficient monitoring of the progress of the reaction by NMR spectroscopy and to avoid the possible decomposition of the product during the workup, again a deuterated solvent was used, namely 90% v/v deuterated acetone/water. In one experiment, triethylamine (Et$_3$N) and in the other, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was present. In both cases, the consumption of the substrate could be observed. A product could not be fully characterised in the case of the experiment with DBU.

In the presence of Et$_3$N, the solvolysis proceeded slower than in the presence of DBU and the product was identified to be [exo-bicyclo[1.1.0]but-2-ylmethyl]-triethylammonium tosylate ($47$, Scheme 47). The experiment was spectroscopically
monitored over a period of 118 days, after which time the tosylate 28 had been consumed to the extent of 76% and 47 had formed in 41% yield. These numbers clearly show that either 28 or 47 or both decompose slowly under the reaction conditions. At the same time, 1-butyl tosylate was transformed to (1-butyl)triethylammonium tosylate. The ratio of 28 and 1-butyl tosylate remained constant over 118 days, demonstrating that the rate constants for both compounds are about the same.

As to the mechanism of the nucleophilic substitutions of 28, the experiments described cannot give a clear-cut answer. In [D₄]methanol in the presence of sodium [D₃]methoxide, 28 and 1-butyl tosylate reacted with the same rate constants. Lower concentrations of the reactants resulted in rate constants reduced by the same factor for 28 and 1-butyl tosylate. Since 1-butyl tosylate cannot undergo an S₁ process, an S₂ process is likely for 28 as well. The transition state can be represented by 48 in Scheme 48. On the other hand, Bentley* has found that the variation of the concentration of triethylamin has only a small effect on the methanolysis rate of 28. This result favours an S₁ reaction of 28 with the classical carbocation 49 (Scheme 48) as intermediate.

3.2.2.3. Kinetic Studies

The rate constants of the solvolyses of the mesylate 24 and the tosylate 28 were determined conductometrically* and are presented in Table 11.

The comparing of the rate constant of mesylate 24 in 60% v/v acetone/water at 25 °C with that of cyclopropylcarbinyl mesylate under the same conditions (k = 5.25 x 10⁻³)₈⁹ shows that the latter reacts three times as fast as the former. Relative to the rate constant of the dimesylate endo,endo-9 (k = 8.2 x 10⁻⁵), that of cyclopropylcarbinyl

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* I thank Dr. T. W. Bentley, University of Wales, Swansea, for communicating these results.
mesylate is 64 times as high.\textsuperscript{80} The rate-retarding effect of the extra mesyloxymethyl group in \textit{endo,endo-9} amounts to a factor of 21 relative to \textbf{24}.\textsuperscript{80}

\textbf{Table 11.} Rate constants for solvolyses of compounds \textbf{24} and \textbf{28} (60\% A = 60\% v/v acetone/water)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Solvent</th>
<th>T [\textdegree C]</th>
<th>(k \text{ [s}^{-1})]</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textbf{24}</td>
<td>60 % A</td>
<td>25</td>
<td>(1.75 \times 10^{-3})</td>
</tr>
<tr>
<td></td>
<td>methanol</td>
<td>25</td>
<td>(1.42 \times 10^{-4})</td>
</tr>
<tr>
<td></td>
<td></td>
<td>40</td>
<td>(8.65 \times 10^{-4})</td>
</tr>
<tr>
<td>\textbf{28}</td>
<td>60 % A</td>
<td>25</td>
<td>(5 \times 10^{-7})</td>
</tr>
<tr>
<td></td>
<td>methanol</td>
<td>40</td>
<td>(3 \times 10^{-6})</td>
</tr>
</tbody>
</table>

The result for the mesylate \textbf{24} in methanol at 25 \textdegree C corresponds to a half-life of ca. 80 min, which is in fair agreement with initial data calculated from the NMR spectra measured for the solvolysis in [D\textsubscript{4}]methanol in the presence of [D\textsubscript{3}]methoxid at 22 \textdegree C. The rise of temperature from 25 to 40 \textdegree C, accelerates the solvolysis of compound \textbf{24} in methanol by a factor of about 6.

The dimesylate \textit{exo,exo-9}\textsuperscript{80} reacts 20 times as fast as the \textit{exo}-tosylate \textbf{28}. In view of a rate factor of less than two between a tosylate and the corresponding mesylate,\textsuperscript{98} the factor of 20 represents the correct order of magnitude for the ratio of the solvolysis rates of the ditosylate corresponding to \textit{exo,exo-9} and \textbf{28}. Surprisingly, the extra mesyloxymethyl group of \textit{exo,exo-9} has a rate-accelerating and thus opposite effect as compared to that of \textit{endo,endo-9}.

In particular, the rate ratios at 25 \textdegree C of the pairs of \textit{endo,endo-9}/\textit{exo,exo-9},\textsuperscript{80} \textit{endo-10}/\textit{exo-10},\textsuperscript{81} and \textbf{24}/\textbf{28} are worthy of note: 8 (40\% aqueous acetone), 0.5 (80\% aqueous dioxane), and 3500 (60\% aqueous acetone), respectively. In methanol as solvent at 40 \textdegree C, the rate ratio of \textbf{24} and \textbf{28} is about 300. These numbers along with the types of the solvolysis products clearly show that \textit{endo,endo-9}, \textit{exo,exo-9}, \textbf{24}, and \textbf{28} behave consistently. However, the rate ratio of \textbf{endo-10} and \textit{exo-10} as well as the type of product described for the reaction of \textit{exo-10}\textsuperscript{81} are at variance with the above reactivity pattern, which is why doubts are justified as to the reliability of these results.
4. Conclusions

1. The stereoselective synthesis of 6 new brominated spiro-1,3-dioxane compounds were carried out in good yields and the structure of the compounds was established using high resolution NMR investigations and the molecular structure of two compounds obtained by single-crystal X-ray diffractometry. The stereoselectivity of the process was explained on the basis of the mechanism of the bromination reaction and on the results of molecular mechanic calculations.

2. The itinerary of the stereoselective dibromination reaction of spiro-1,3-dioxanes was elucidated on the basis of the structure of 5 monobrominated precursors and was proved by the reaction of these compounds with bromine.

3. The structural investigations revealed the anancomeric structure of the compounds and the preference of brominated derivatives for the “bromine outside” conformers.

4. A complete series of new macrocyclic compounds (10 compounds) was obtained in very good yields using the high dilution method and starting from spiro-1,3-dioxanes bearing phenol groups. The yields and the ratios between the monomer and dimer macrocycles resulted in the syntheses carried out using ditosylated and dibrominated polyethyleneglycols were critically compared.

5. The structure of macrocycles was established using complex NMR investigations, FAB and MALDI mass spectrometry investigations and the molecular structure in single crystal of three compounds obtained by X-ray diffractometry. The NMR spectra showed the anancomeric structure of all derivatives and the equatorial disposition of the aromatic ring.

6. The molecular structure of the monomer with six ethyleneoxy units showed the inclusion in the macrocycle of a molecule of water. Supramolecular interactions by hydrogen bonds between the included molecule of water and the oxygen atoms of the chain were revealed.

7. The molecular structure of the dimer with four ethyleneoxy units suggests a macrocyclic system with two virtual two cavities, which can be used as a ditopic ligand.

8. The FAB and MALDI mass spectrometry investigations showed the high coordination capacity for Na and K cations of investigated macrocycles as monotopic and as ditopic ligands.
9. The synthesis of 2 new bicyclobutane alcohols (endo and exo isomers) was performed using diastereospecific and diastereoselective cyclization reactions.

10. The different course of the solvolysis reaction (as products and as mechanism) of the sulfonates derivatives of the two alcohol isomers was proved by the structure of the products of the solvolysis and by kinetic measurements.

11. The synthesis and the solvolyses studies of the two bicyclobutane alcohols required the synthesis of another 7 new bicyclobutane derivatives and intermediary compounds. All these compounds were fully analyzed and characterized.

12. The literature concerning the bromination of cyclic acetals, and of macrocyclic compounds exhibiting sugar units or bicyclodecane units as well as the literature concerning the structure, synthesis and reactivity of bicyclobutane derivatives were reviewed.
Selective References

Part A

Part B
82. W. Tischer, Dissertation, Universität München, 1991. I thank Prof. G. Szeimies for making this information available.