α-Heterosubstituted phosphonates and phosphinoxides

Marian Mikołajczyk
Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, Department of Organic Sulfur Compounds, 90-362 Łódź, Boczna 5, Poland

Abstract - 1H, 13C, 31P NMR, and X-ray crystallographic studies revealed a strong axial preference of the phosphoryl group in the 1,3-di- and 1,3,5-trithiane ring. Chemical equilibration of ananomeric pairs of the dithianes 14–17 showed that axial preference decreases in the order: (MeO)2P(0)Ph2P(0)Ph2P(S)Ph2P(Se). The nature of S-C-P anomeric interactions is discussed.

INTRODUCTION

The development of new synthetic reagents containing heteroatoms such as phosphorus, sulfur, and silicon has attracted great attention of many research groups (ref. 1 to 3). Due to the presence of heteroatoms, such reagents are suitable for further transformations and especially useful in reversal (Um-polung) of normal reactivity of nucleophilic and electrophilic centers (ref. 4). Our interest in this area was focused on the phosphonates which contain additionally other heteroatomic functional groups at the α-carbon atom. These compounds are interesting from both synthetic and stereochemical points of view. α-Phosphoryl sulphoxides 1, which have been obtained in our laboratory a long time ago (ref. 5), play an important role as reagents for the synthesis of racemic and chiral α,β-unsaturated sulphoxides (ref. 6,7) as well as model compounds in the studies of asymmetric induction on the α-carbon atom (ref. 8). Acyclic and cyclic S,S-thioacetals of formylphosphonates 2 have also been synthesized by us in collaboration with the group of Professor H.Gross from GDR (ref. 9,10). The Horner reaction of 2 with carbonyl compounds was found to be a general reaction leading to ketene S,S-thioacetals (ref. 11,12). Another interesting example of α-heterosubstituted phosphonate is α-methylthiovinylphosphonate 3 (ref. 13) which represents a new acetyl anion equivalent shown below. Vinylphosphonate 3 is a key compound for the synthesis of α-methylthio substituted ketones (ref. 14) and methylenomycin B (ref. 13).

Recently, we have also succeeded in the preparation of the phosphonate 4 bearing the alkylthio and trimethylsilyl groups at the α-carbon (ref. 15). In contrast to α-phosphoryl sulfoxides 1 and thioacetals 2, this phosphonate reacts with aldehydes under basic conditions to give vinylphosphonates i.e. the Peterson reaction products. It should be noted that the other synthetically useful phosphonates were also recently prepared in the course of our studies on synthesis of 1,4-dicarbonyl compounds and functionalized cyclopentenones (ref. 16,17).

This account, however, is concerned with some conformational problems of cyclic six-membered, dithioacetals 2 and related compounds. Our interest in this area was stimulated by the fact that cyclic and acyclic 2 show different reactivity towards electrophilic reagents. Moreover, the conformation of cyclic dithioacetals 2 was of importance in connection with the anomeric effect operating in some 2-substituted 1,3-dithianes (ref. 18). The first evidence that the 2-diphenylphosphinoyl group is axial in 1,3-dithiane 5 was provided by
Soon after that, we found that 2-dimethoxyphosphoryl group occupies an axial position in 1,3,5-trithiane 6 (ref. 20) and 1,3-thiane 7 (ref. 21).

However, explanation of this anomeric effect is at present far from satisfactory (ref. 22). The aim of our studies was to find convenient methods for a fast assignment of axial or equatorial position of the organophosphorus substituents in dithianes and to get better insight into the nature of the S-C-P anomeric interactions. The results obtained are presented below.

SYNTHESIS OF 2-PHOSPHORYL, 2-THIOPHOSPHORYL AND 2-SELENOPHOSPHORYL 1,3-DITHIANES AND RELATED COMPOUNDS

The synthesis of 2-phosphoryl-1,3-dithianes and 1,3,5-trithianes was accomplished by the method described by us earlier (ref. 9,10) which involves the reaction of 2-chloro-1,3-dithiane (or 1,3,5-trithiane) with trivalent phosphorus compounds. In this way, we prepared (ref. 23) phosphinoxides 8-10 which were easily converted into their thiophosphoryl analogues 11-13 upon treatment with phosphorus pentasulfide (Scheme I).

The same method has been applied for the synthesis of cis- and trans isomers of 2-(dimethoxyphosphoryl)-5-t-butyl-1,3-dithiane 14 and its 2-diphenylphosphino analogue 15 (Scheme II). Thus, the reaction of 2-chloro-5-t-butyl-1,3-dithiane with trimethyl phosphite gave a mixture of cis- and trans-14 in a 7:1 ratio. A similar reaction with isopropyl diphenylphosphinite afforded the corresponding cis-15 and trans-15 in a 3:1 ratio. The anomers of 14 and 15 were easily separated by column chromatography on silica gel. It is interesting to note that trans-14 is formed as a major isomer when 4-t-butyl-1,2-dithiolane was reacted with dimethyl diazomethane phosphonate.
Scheme III shows the method of preparation of the pure anancomers of 16 and 17 i.e. 2-thiophosphoryl and 2-selenophosphoryl 1,3-dithiane derivatives. Treatment of cis-15 and trans-15 with $\text{P}_4\text{S}_{10}$ resulted in a clean conversion into cis-16 and trans-16, respectively. The synthesis of both anancomeric selenium compounds 17 was accomplished via the corresponding phosphines 18 obtained in a stereo-selective way as shown below. Addition of selenium to 18 gave the desired cis- and trans-17.

![Scheme III](image)

**CONFORMATIONAL ANALYSIS OF 2-PHOSPHORYL, 2-THIOPHOSPHORYL, AND 2-SELENOPHOSPHORYL 1,3-DITHIANES AND 1,3,5-TRITHIANES**

Conformation of anancomeric pairs of dithianes 14-17

Conformation of cis- and trans-isomers of the dithianes 14-17 prepared as shown above was determined by $^1$H-NMR spectroscopy. The proton NMR spectra (250 MHz) of the compounds under discussion are conclusive and allow to assign unambiguously an axial and equatorial position for the organophosphorus substituent at C-2. The coupling constants of the methylene protons with the methine proton at C-5 as well as with phosphorus are diagnostic. As expected, axial methylene protons at C-4 and C-6 of cis-isomers appear in the proton NMR spectra at lower field due to the deshielding effect of the axial R$_2$P(X)-group and show a coupling with phosphorus. The chemical shift difference between the axial and equatorial protons at C-4 and C-6 is about 1 ppm. On the other hand, the $\Delta$ value estimated for trans-isomers is smaller than 0.5 ppm and the equatorial methylene protons absorb at lower field. Our NMR configurational assignments to anancomeric dithianes 14-17 were definitively confirmed by X-ray analysis of cis-15. A perspective view of the molecular structure is shown in Fig. 1. The six-membered ring exists in a chair conformation with the Ph$_2$P(O)-group being axial.

Analysis of the $^{13}$C-NMR spectra of anancomeric pairs of the dithianes 14-16 and the compounds 5-7, for which conformational preferences have been established earlier, indicated that there is a clear relationship between the position of the P-substituent at C-2 and the $\gamma$-effect value and the coupling constant $^3$CP. Thus, the $\gamma$-effect is negative and the coupling constant $^3$PC-P is nearly zero for the dithianes with the axial phosphorus substituent. When the P(O) or P(S)-group is located in the equatorial position the $\gamma$-effect values are positive or nearing to zero and the coupling constant $^3$PC-P is about 7-10 Hz.

**TABLE 1. Values of $T_1$ and $T_2$ for anancomeric dithianes 14-16**

<table>
<thead>
<tr>
<th>No</th>
<th>$T_1$ (ms)</th>
<th>$T_2$ (ms)</th>
<th>$\rho_{ax}$</th>
<th>$\rho_{eq}$</th>
<th>$\gamma$-effect value</th>
<th>$\rho$-effect value</th>
</tr>
</thead>
<tbody>
<tr>
<td>cis-14</td>
<td>9.93</td>
<td>0.68</td>
<td>18.03</td>
<td>3.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-14</td>
<td>10.59</td>
<td>0.23</td>
<td>56.86</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-15</td>
<td>5.37</td>
<td>0.79</td>
<td>8.37</td>
<td>4.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-15</td>
<td>5.67</td>
<td>0.18</td>
<td>38.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cis-16</td>
<td>10.02</td>
<td>0.93</td>
<td>13.31</td>
<td>4.92</td>
<td></td>
<td></td>
</tr>
<tr>
<td>trans-16</td>
<td>10.60</td>
<td>0.20</td>
<td>69.46</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$\eta$-NOE enhancement coefficient; $\rho$-relaxation for intramolecular dipolar mechanism

Fig. 1. Perspective view of the molecular structure of cis-15
Finally, it should be pointed out that measurements of the $^{31}$P spin-lattice relaxation time and NOE for the dithianes 14-16 allow to calculate the $T_{1\text{DD}}$ values which are substantially different for cis- and trans-isomers. Table 1 summarizes the results so far obtained.

Conformation of di- and trithianes 8-13 and 2-(diphenylphosphinoyl)-5,5-dimethyl-1,3-dioxane 19

Based on the NMR spectral criteria ($\Delta A, \gamma$-effect, $3J_{CP}$) discussed above one may propose that the $\text{PhP(O)}$-group in 8-9 is almost exclusively axial whereas the thiophosphoryl derivatives 10-13 exist in a solution as a mixture of axial and equatorial conformers in comparable amounts because both the $\gamma$-effect and $3J_{CP}$ values are mean values. This assumption was supported by our observation that the $^{31}$P NMR signal for 11 is split at $-100^\circ\text{C}$ into two lines of similar intensity which correspond most probably to axial and equatorial conformers of 11. In this context, it is interesting to add that the trithiane-11 adopts in the crystal a chair conformation with the PhP(S)-group being equatorial (Fig. 2). In contrast to a strong axial preference of the PhP(0)-group in di- and trithianes, it was found that in 1,3-dioxane 19 it occupies the equatorial position both in solution and in the solid state (see Fig. 3).

Base-catalyzed equilibration of anamomeric pairs of dithianes 14-17

In order to estimate the magnitude of the anamomeric effect operating in 1,3-dithianes and 1,3,5-trithianes with the P-substituent at the anamomeric position as well as to determine quantitatively the effect of replacement of the phosphoryl oxygen by sulphur and selenium, the base-catalyzed equilibration of cis- and trans-isomers of 14-17 was studied. It was found that both pure cis- and trans-isomers undergo equilibration in the presence of sodium methoxide in methanol solution at room temperature. The progress of this process was followed by $^{31}$P($^1$H)NMR spectra which allowed also to determine the diastereomeric ratios at equilibrium with a good accuracy. The experimental results obtained and the calculated conformational free energy differences, $\Delta G^\circ$, are summarized in Table 2.

An inspection of the results in Table 2 clearly shows that the tendency to occupy an axial position in the heterocyclic 1,3-dithiane ring is strongest for the phosphoryl group and decreases on going to the thiophosphoryl and then to selenophosphoryl group. In accord with the data of Juaristi et al. (ref. 22,24) on the magnitude of the anamomeric effect in 5 estimated as ca. 3.75 kcal/mol, the anamomeric effect operative in our systems has a similar value.
TABLE 2. Equilibration of anancomeric pairs of dithianes 14—17

<table>
<thead>
<tr>
<th>Compounds, R₂P(X)</th>
<th>cis:trans ratio at equilibrium</th>
<th>K [kJ/mol]</th>
<th>ΔG° [kJ/mol]</th>
</tr>
</thead>
<tbody>
<tr>
<td>14, (MeO)₂P(O)</td>
<td>88.3:11.7</td>
<td>7.54</td>
<td>4.92</td>
</tr>
<tr>
<td>15, Ph₂P(O)</td>
<td>83.4:16.6</td>
<td>5.02</td>
<td>3.93</td>
</tr>
<tr>
<td>16, Ph₂P(S)</td>
<td>70.2:29.8</td>
<td>2.36</td>
<td>2.09</td>
</tr>
<tr>
<td>17, Ph₂P(Se)</td>
<td>64.4:35.6</td>
<td>1.81</td>
<td>1.47</td>
</tr>
</tbody>
</table>

DISCUSSION ON THE ORIGIN OF THE ANOMERIC EFFECT IN P-SUBSTITUTED DI- AND TRITHIANES

Although our program aimed at elucidation of conformational preferences of various organophosphorus substituents in heteroanes is not completed, the results so far obtained allow to make some comments on the origin of the anomeric effect in 2-phosphoryl-1,3-dithianes and their P(S) and P(Se) analogues. Generally, the anomeric effect is interpreted in terms of delocalization of the lone pair on the endocyclic heteroatom into the antiperiplanar adjacent polar bond (ref. 27). In our case δS—GC_p interactions should be taken into account. However, if this effect were operative, one should expect a shortening of S—C(2) and elongation of C(2)—P bond distances in axial vs. equatorial isomers. The X-ray data of the P-substituted 1,3-di-, 1,3,5-trithianes and 1,3-dioxane collected by us and Juaristi et al. (Table 3) reveal that the observed lengths are normal and the expected changes characteristic for the anomeric effect are not visible.

TABLE 3. Selected bond lengths (Å)

<table>
<thead>
<tr>
<th>Bond</th>
<th>5</th>
<th>6</th>
<th>cis-15</th>
<th>11</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>S—C(2)</td>
<td>1.809</td>
<td>1.810</td>
<td>1.845</td>
<td>1.822</td>
<td>-</td>
</tr>
<tr>
<td>C(2)—P</td>
<td>1.825</td>
<td>1.812</td>
<td>1.824</td>
<td>1.829</td>
<td>1.846</td>
</tr>
</tbody>
</table>

Therefore, the observed strong preference of the phosphoryl group may be due to other effects. The molecular mechanics calculations [carried out by Kabachnik and Baranov (ref. 28)] of the two possible chair conformers of the trithiane 8 showed that their energy is equal if the electrostatic interactions between non-bonded electron pairs on sulfur and on phosphoryl oxygen are neglected. However, if this type of repulsive interactions is taken into account, the energy of the axial conformer is smaller than that of the equatorial one by about 5.7—8.3 kJ/mol. This value is in excellent agreement with those obtained from the equilibration experiments.

According to our original proposal (ref. 20) the axial position of the phosphoryl group may be additionally stabilized by attractive interactions between the phosphoryl oxygen atom and the axial hydrogens at C-4 and C-6 having a character of very weak hydrogen bonds. This is due to the fact that the phosphoryl oxygen atom is almost symmetrically situated above the heterocyclic ring. Such a situation was found for the trithiane 6 and cis-15. In the case of the axial thiophosphoryl group, the interactions of the axial hydrogens with sulfur, which is much bigger than oxygen, and of lower electronegativity, may be expected to be repulsive in character leading consequently to destabilization of the axial P(S)-conformer. This effect is even more pronounced for the selenophosphoryl group, which shows the lowest bias towards axial position.

In summary it is believed that conformational preferences of the P(O), P(S) and P(Se)- group in di- and trithianes are controlled by special kind of electronic interactions and steric effects. This proposal needs, however, further studies and other systems are currently investigated.
Acknowledgements - I wish to express my thanks to my coworkers Dr P. Balczewski, Mr P. Graczyk and Dr. K. Wróblewski who have contributed to the development of the work described in this paper. I am especially grateful to Dr. M. Wieczorek (Institute of General Chemistry, Technical University, Łódź) and Prof. Y. T. Struchkov (Institute of Elementoorganic Compounds, Academy of Sciences, USSR, Moscow) for X-ray structural analyses as well as to Prof. M. I. Kabachnik (Institute of Elementoorganic Compounds) for his interest in this work and for calculations. I also thank the Polish Academy of Sciences for a financial support of this work within the project CPBP-01.13.

REFERENCES