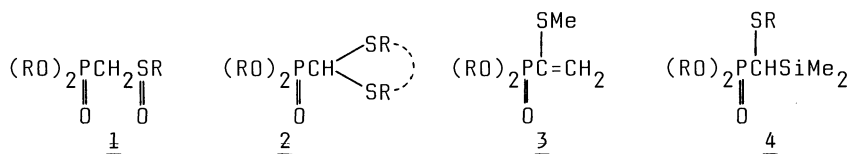# α-Heterosubstituted phosphonates and phosphinoxides

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Abstract - ^{1}H, ^{13}C, ^{31}P 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 anancomeric pairs of the dithianes 14-17 showed that axial
preference decreases in the order: $(MeO)_2P(O) > Ph_2P(O) >$
$Ph_2P(S) > Ph_2P(Se)$. The nature of S-C-P anomeric interactions
is discussed.

INTRODUCTION

The development of new synthetic reagents containing heteroatoms such as phos-
phorus, 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 synthe-
sis 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-me-
thylthiovinylphosphonate 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).

$$(RO)_2\underset{\underset{O}{\|}}{P}CH_2SR \qquad (RO)_2\underset{\underset{O}{\|}}{P}CH\overset{SR}{\underset{SR}{<}} \qquad (RO)_2\underset{\underset{O}{\|}}{P}\overset{SMe}{\overset{|}{C}}=CH_2 \qquad (RO)_2\underset{\underset{O}{\|}}{P}\overset{SR}{\overset{|}{C}}HSiMe_2$$

$$\underline{1} \qquad\qquad \underline{2} \qquad\qquad \underline{3} \qquad\qquad \underline{4}$$

Recently, we have also succeeded in the preparation of the phosphonate 4 be-
aring the alkylthio and trimethylsilyl groups at the α-carbon (ref. 15). In
contrast to α-phosphoryl sulphoxides 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 syntheti-
cally useful phosphonates were also recently prepared in the course of our
studies on synthesis of 1,4-dicarbonyl compounds and functionalized cyclo-
pentenones (ref. 16,17).

This account, however, is concerned with some conformational problems of cyc-
lic six-membered, dithioacetals 2 and related compounds. Our interest in this
area was stimulated by the fact that cyclic and acyclic 2 show different re-
activity towards electrophilic reagents. Moreover, the conformation of cyclic
dithioacetals 2 was of importance in connection with the anomeric effect ope-
rating 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

Juaristi et al. (ref. 19). Soon after that, we found that 2-dimethoxyphospho-
ryl group occupies an axial position in 1,3,5-trithiane $\underline{6}$ (ref. 20) and 1,3-
-thiane $\underline{7}$ (ref. 21).

$$O=PPh_2 \qquad O=P(OMe)_2 \qquad O=P(OMe)_2$$

$$\underline{5} \qquad\qquad \underline{6} \qquad\qquad \underline{7}$$
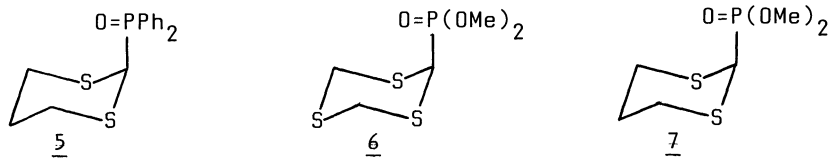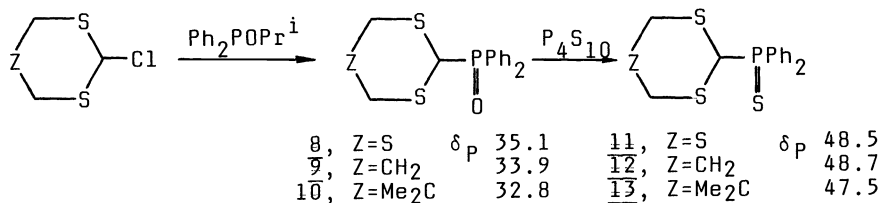
However, explanation of this anomeric effect is at present far from satisfac-
tory (ref. 22). The aim of our studies was to find convenient methods for a
fast assignment of axial or equatorial position of the organophosphorus subs-
tituents in dithianes and to get better insight into the nature of the S-C-P
anomeric interactions. The results obtained are presented below.

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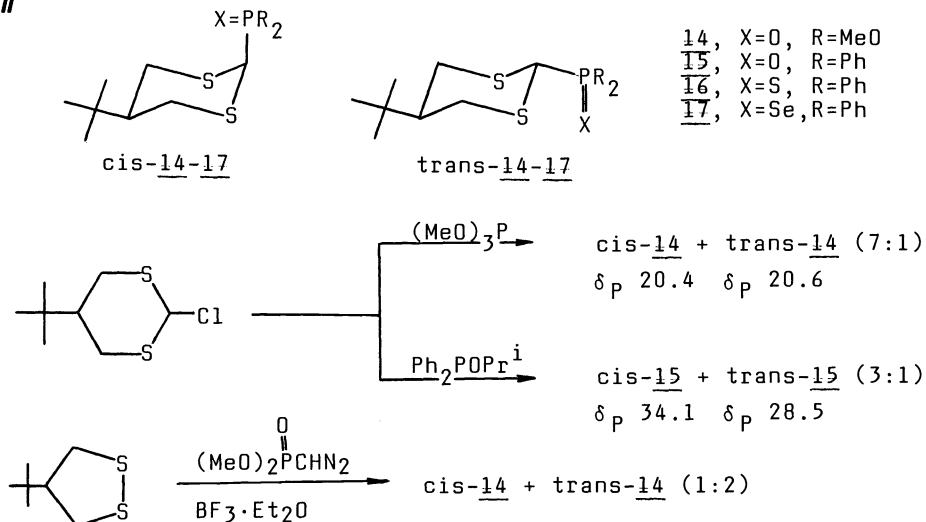## 2-SELENOPHOSPHORYL 1,3-DITHIANES AND RELATED COMPOUNDS

The synthesis of 2-phosphoryl-1,3-dithianes and 1,3,5-trithianes was accompli-
shed 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 phos-
phorus compounds. In this way, we prepared (ref. 23) phosphinoxides $\underline{8}$-$\underline{10}$ which
were easily converted into their thiophosphoryl analogues $\underline{11}$-$\underline{13}$ upon treatment
with phosphorus pentasulfide (Scheme I).

Scheme I

$$Z \overset{S}{\underset{S}{\diamond}} -Cl \xrightarrow{Ph_2POPr^i} Z \overset{S}{\underset{S}{\diamond}} -\underset{\underset{O}{\parallel}}{P}Ph_2 \xrightarrow{P_4S_{10}} Z \overset{S}{\underset{S}{\diamond}} -\underset{\underset{S}{\parallel}}{P}Ph_2$$

|		δ_P			δ_P
$\underline{8}$,	Z=S	35.1	$\underline{11}$,	Z=S	48.5
$\underline{9}$,	Z=CH$_2$	33.9	$\underline{12}$,	Z=CH$_2$	48.7
$\underline{10}$,	Z=Me$_2$C	32.8	$\underline{13}$,	Z=Me$_2$C	47.5

The same method has been applied for the synthesis of cis- and trans isomers
of 2-(dimethoxyphosphoryl)-5-t-butyl-1,3-dithiane $\underline{14}$ and its 2-diphenylphos-
phinoyl analogue $\underline{15}$ (Scheme II). Thus, the reaction of 2-chloro-5-t-butyl-
-1,3-dithiane with trimethyl phosphite gave a mixture of cis- and trans-$\underline{14}$
in a 7:1 ratio. A similar reaction with isopropyl diphenylphosphinite affor-
ded the corresponding cis-$\underline{15}$ and trans-$\underline{15}$ in a 3:1 ratio. The anancomers of
$\underline{14}$ and $\underline{15}$ were easily separated by column chromatography on silica gel. It is
interesting to note that trans-$\underline{14}$ is formed as a major isomer when 4-t-butyl-
-1,2-dithiolane was reacted with dimethyl diazomethanephosphonate.

Scheme II

$$X=PR_2$$

cis-$\underline{14}$-$\underline{17}$ $\qquad\qquad$ trans-$\underline{14}$-$\underline{17}$

$\underline{14}$,	X=O,	R=MeO
$\underline{15}$,	X=O,	R=Ph
$\underline{16}$,	X=S,	R=Ph
$\underline{17}$,	X=Se,	R=Ph

$$\xrightarrow{(MeO)_3P} \text{cis-}\underline{14} + \text{trans-}\underline{14} \ (7:1)$$
$$\delta_P \ 20.4 \quad \delta_P \ 20.6$$

$$\xrightarrow{Ph_2POPr^i} \text{cis-}\underline{15} + \text{trans-}\underline{15} \ (3:1)$$
$$\delta_P \ 34.1 \quad \delta_P \ 28.5$$

$$\xrightarrow[BF_3 \cdot Et_2O]{(MeO)_2\overset{O}{\overset{\parallel}{P}}CHN_2} \text{cis-}\underline{14} + \text{trans-}\underline{14} \ (1:2)$$

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 P_4S_{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 stereoselective way as shown below. Addition of selenium to 18 gave the desired cis- and trans-17.

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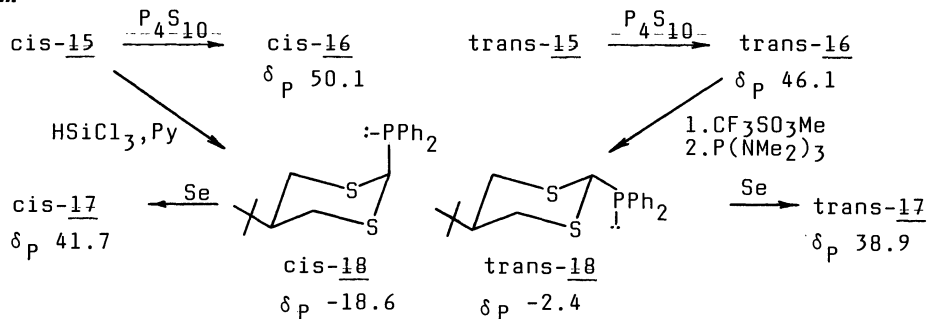
CONFORMATIONAL ANALYSIS OF 2-PHOSPHORYL, 2-THIOPHOSPHORYL
AND 2-SELENOPHOSPHORYL 1,3-DITHIANES AND 1,3,5-TRITHIANES

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 unambigously 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 $R_2P(X)$-group and show a coupling with phosphorus. The chemical shift difference;Δδ between the axial and equatorial protons at C-4 and C-6 is about 1 ppm.On the other hand, the Δδ-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 $Ph_2P(O)$-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 γ-effect value and the coupling constant $^3J_{C-P}$. Thus, the γ-effect is negative and the coupling constant $^3J_{C-P}$ 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 γ-effect values are positive or nearing to zero and the coupling constant $^3P_{C-P}$ is about 7-10 Hz.
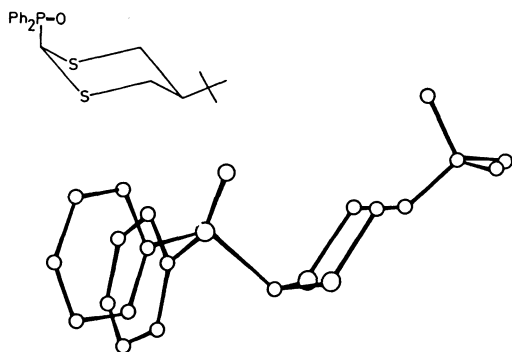
TABLE 1. Values of T_1, , and T_1^{DD} for anancomeric dithianes 14-16

No	T_1^{OBS}	η	T_1^{DD}	$\rho_{ax}^{DD}/\rho_{eq}^{DD}$
cis-14	9.93	0.68	18.03	3.15
trans-14	10.59	0.23	56.86	
cis-15	5.37	0.79	8.37	4.65
trans-15	5.67	0.18	38.9	
cis-16	10.02	0.93	13.31	4.92
trans-16	10.60	0.20	65.46	

η-NOE enhancement coefficient; ρ^{DD}- 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^{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 ($\delta\Delta$,γ-effect,$^3J_{C-P}$) discussed above one may propose that the Ph$_2$P(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 γ-effect and $^3J_{C-P}$ values are mean values. This assumption was supported by our observation that the ^{31}P NMR signal for 11 is split at -100°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 Ph$_2$P(S)-group being equatorial (Fig. 2). In contrast to a strong axial preference of the Ph$_2$P(O)-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).
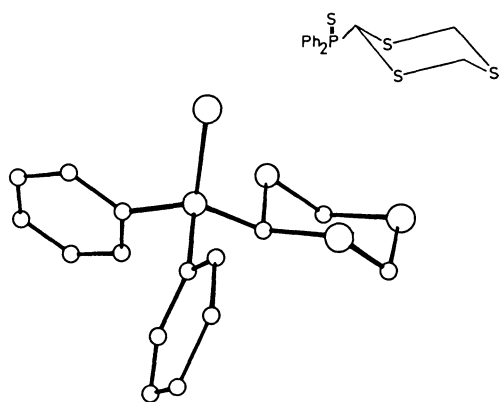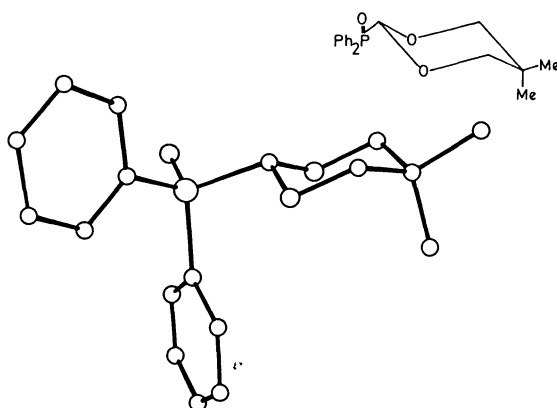
Fig. 2. Perspective view of the mole-   Fig. 3. Perspective view of the mole-
cular structure of 11   cular structure of 19

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

In order to estimate the magnitude of the anomeric effect operating in 1,3--dithianes and 1,3,5-trithianes with the P-substituent at the anomeric 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 diastereoisomeric 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.
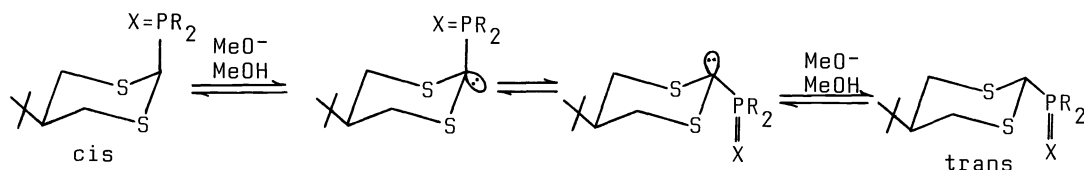
An inspection of the results in Table 2 clearly shows that the tendency to occupy an axial position in the heterocyclic 1,3-dithiane ring is strongest for the phosphoryl group and decreases on going to the thiophosphoryl and then to selenophosphoryl group. In accord with the data of Juaristi et al. (ref. 22,24) on the magnitude of the anomeric effect in 5 estimated as ca. 3.75 kcal/mol, the anomeric effect operative in our systems has a similar value.

TABLE 2. Equilibration of anancomeric pairs of dithianes <u>14</u>-<u>17</u>

Compounds, $R_2P(X)$	cis:trans ratio at equilibrium	K	ΔG^0 [kJ/mol]
<u>14</u>,(MeO)$_2$P(O)	88.3:11.7	7.54	4.92
<u>15</u>,Ph$_2$P(O)	83.4:16.6	5.02	3.93
<u>16</u>,Ph$_2$P(S)	70.2:29.8	2.36	2.09
<u>17</u>,Ph$_2$P(Se)	64.4:35.6	1.81	1.47

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 ano-
meric effect in 2-phosphoryl-1,3-dithianes and their P(S) and P(Se) analogues.
Generally, the anomeric effèct 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 n_S-σ_{C-P} interactions should be taken into
account. However, if this effect were operative, one should expect a shorte-
ning of S-C(2) and elongation of C(2)-P bond distances in axial vs. equato-
rial 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)

Bond	<u>5</u>	<u>6</u>	cis-<u>15</u>	<u>11</u>	<u>19</u>
S-C(2)	1.809	1.810	1.845	1.822	–
C(2)-P	1.825	1.812	1.824	1.829	1.846

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 <u>8</u> showed that their energy is equal if the electrostatic interac-
tions 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 equa-
torial one by about 5.7-8.3 kJ/mol. This value is in excellent agreement with
those obtained from the equilibration experiments.

ax-<u>8</u>   eq-<u>8</u>
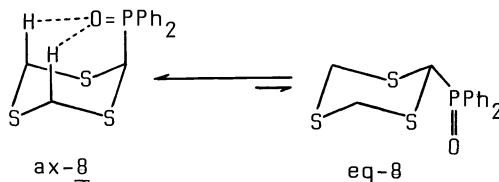
According to our original proposal (ref. 20) the axial position of the phos-
phoryl group may be additionally stabilized by attractive interactions between
the phosphoryl oxygen atom and the axial hydrogens at C-4 and C-6 having a
character of very weak hydrogen bonds. This is due to the fact that the phos-
phoryl oxygen atom is almost symmetrically situated above the heterocyclic
ring. Such a situation was found for the trithiane <u>6</u> and cis-<u>15</u>. 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 destabi-
lization of the axial P(S)-conformer. This effect is even more pronounced for
the selenophosphoryl group, which shows the lowest bias towards axial positi-
on.

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.

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