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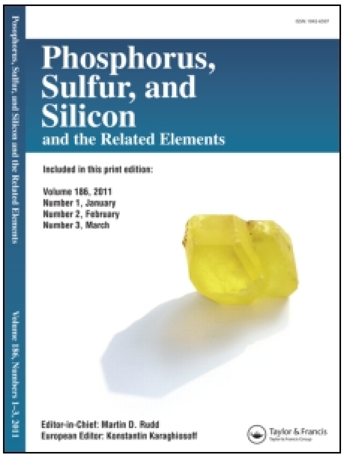

Phosphorus, Sulfur, and Silicon and the Related Elements

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Conformational Studies of 1,3-Dithianes and their Oxo and Seleno Analogues Containing Organophosphorus Substituents. A Question of the Anomeric Effect

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CONFORMATIONAL STUDIES OF 1,3-DITHIANES AND THEIR OXO AND SELENO ANALOGUES CONTAINING ORGANOPHOSPHORUS SUBSTITUENTS. A QUESTION OF THE ANOMERIC EFFECT.

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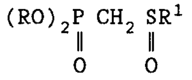
Abstract This review summarizes the results of conformational studies on 2-organophosphorus substituted 1,3-dithianes, 1,3-dioxanes and 1,3-diselenanes. The synthetic approaches to the compounds investigated are briefly presented. The conformation of 2-phosphoryl-, 2-thiophosphoryl- and 2-selenophosphoryl-1,3-diheteroanes was determined by chemical, spectral and X-ray methods. The anomeric effect was found to operate in all compounds studied. Crystallographic, spectroscopic and thermodynamic data suggest the $n_X-\sigma^*_{C-P}$ hyperconjugative interactions as one of the factors responsible for the anomeric effect. The axial preference of the phosphoryl group in 1,3-diheteroanes is also due to hydrogen bond formation between the phosphoryl oxygen and axial hydrogen(s) at C(4) and C(6). The role of repulsive interactions between the lone pairs on endocyclic heteroatoms and on the P=X heteroatoms are also discussed. The operation of the generalized anomeric effect was also found for 2-phosphonio-1,3-dithianes what is in a sharp contrast to the O-C-N^+ system exhibiting the reverse anomeric effect.

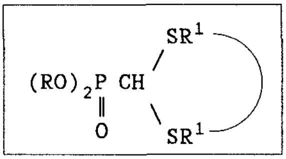
INTRODUCTION

For the past few years, one of the research directions in the author's laboratory has centered on the synthesis, properties and synthetic applications of organic compounds containing both sulfur and phosphorus in one molecule[1]. Some representative examples of such mixed organic sulfur-phosphorus compounds and reagents prepared in our laboratory are shown below.



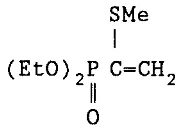
$(RO)_2P(=O)CH_2S(=O)R^1$

A



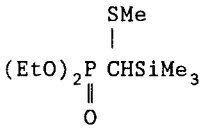
$(RO)_2P(=O)CH(SR^1)_2$

B



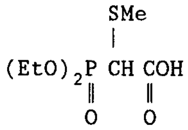
$(EtO)_2P(=O)C(SMe)=CH_2$

C



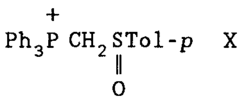
$(EtO)_2P(=O)CH(SMe)SiMe_3$

D



$(EtO)_2P(=O)CH(SMe)C(=O)OH$

E

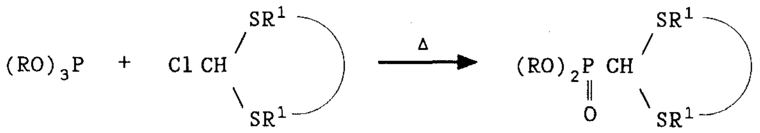


$Ph_3\overset{+}{P}CH_2S(=O)Tol\text{-}p\ X^-$

F

A: α-Phosphoryl sulfoxides[2]
B: S,S-Dithioacetals of formylphosphonates[3]
C: Diethyl α-methylthiovinyl phosphonate[4]
D: Diethyl α-methylthio-α-trimethylsilylmethanephosphonate[5]
E: Diethyl α-methylthiophosphonoacetic acid[6]
F: Triphenylphosphoniomethyl *p*-tolyl sulfoxide[7]

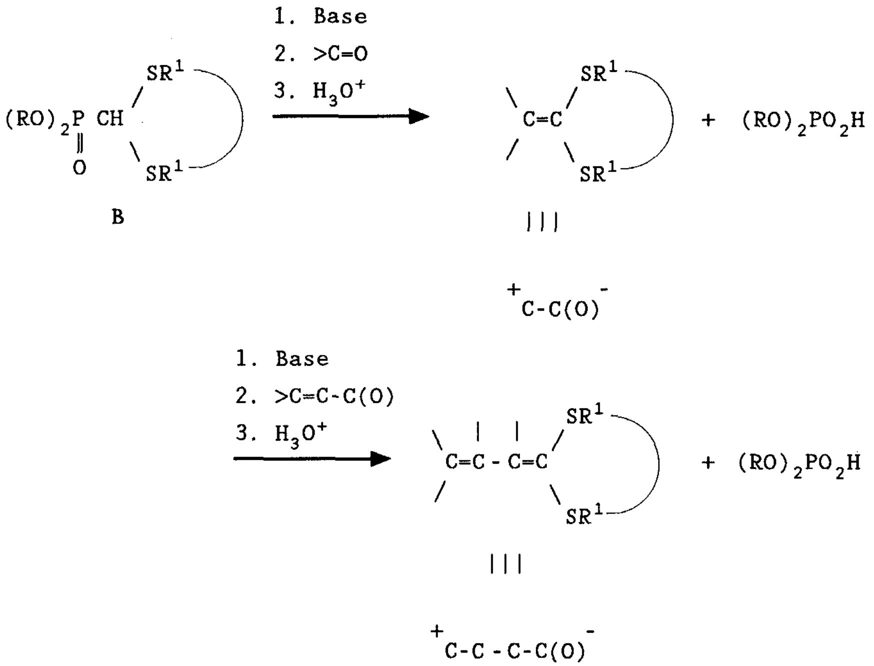
Among them dithioacetals of formylphosphonates **B** deserve particular attention because they represent a rather new class of synthetically useful phosphonates. Various acyclic and cyclic dithioacetals **B** have been first prepared by us in collaboration with the group of Professor H. Gross by the Arbuzov reaction of trialkyl phosphites with chlorodithioacetals (Fig.1).[3] Later on, other synthetic approaches to dithioacetals **B** have been developed.[8,9]



B

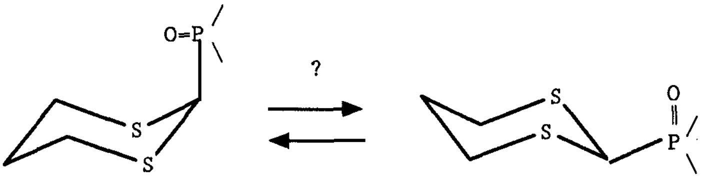
(1)

The Horner reaction of thioacetals **B** with saturated and α,β-unsaturated carbonyl compounds was found to be a general synthesis of simple or conjugated ketene dithioacetals[10] which, in turn, are very useful organic synthons.



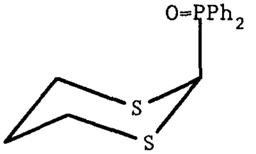
(2)

Our interest in the conformational studies of cyclic six-membered dithioacetals **B** (2-phosphoryl-1,3-dithianes) was stimulated by the fact that acyclic and cyclic dithioacetals **B** show different reactivity towards some electrophilic reagents and, what is perhaps more important, that in some 2-substituted-1,3-dithianes the anomeric effect was found to operate.[11] For example, Ôki and coworkers[12] showed that substituents such as benzyloxy, phenylthio, carboxy and chloro attached to the carbon atom C(2) of the 1,3-dithiane ring strongly prefer the axial position. In view of these results two immediate questions arose: what is the conformational preference of the phosphoryl group bonded to C(2) of the 1,3-dithiane ring? and does the anomeric effect operate also in this system?

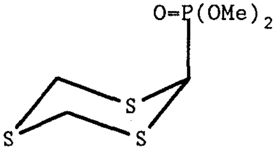


(3)

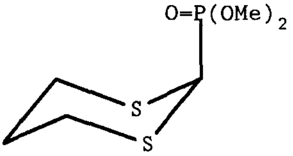
The first evidence that the 2-diphenylphosphinoyl group is axial in 1,3-dithiane **1** was provided by Juaristi *et.al.* in 1982. Soon thereafter, we found that the 2-dimethoxyphosphoryl group shows also a strong preference for the axial position in 1,3,5-trithiane **2**[14] and



1



2



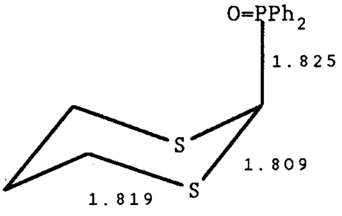
3

1,3-dithiane **3**.[15] Therefore, it became clear that 2-phosphoryl-substituted polythianes represent a new example of the structure in which the anomeric effect is observed*. This finding was, however, rather surprising since both the $Ph_2P(O)$ and $(MeO)_2P(O)$ groups are very bulky and their steric size is greater than or comparable with that of the *t*-butyl group widely used in conformational studies as a holding, equatorial substituent. Moreover, on the phosphorus atom bonded to the anomeric carbon atom in **1-3** there is no lone electron pair and the difference in electronegativity between P and C is rather

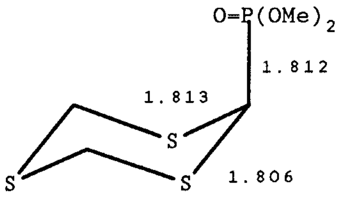
---

*In accord with the definition of the generalized anomeric effect: the general preference for the *gauche* conformation about a carbon-hetero-atom bond in systems R-X-C-Y.

small. More interestingly, the X-ray data of **1**,[13] **2**[14] and *cis*-4,6-dimethyl-2-diphenylphosphinoyl-1,3-dithiane **4** revealed that geometrical parameters in the crystal, especially the S-C and C-P bond distances, did not come up to expectations based on the $n_S-\sigma^*_{C-P}$ negative hyperconjugation . In accord with the commonly accepted view,[11] this type of stereoelectronic effect may be considered to be responsible for the anomeric effect operative in this system.[11]



1



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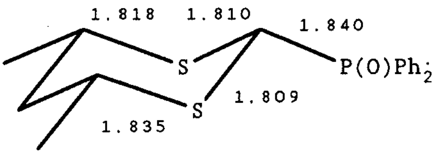
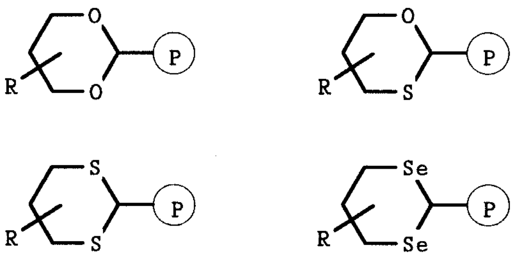


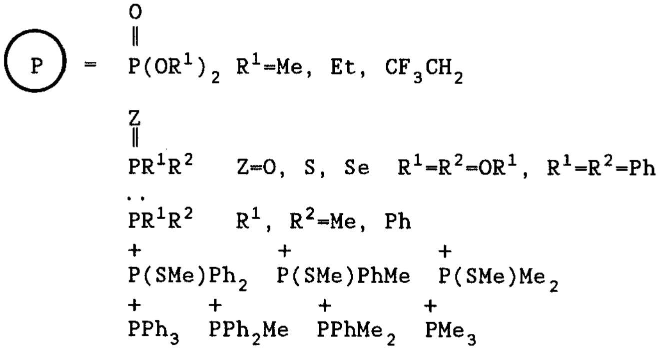
4

In this situation we decided to study the scope, limitations and nature of the X-C-P (X=O, S, Se) anomeric interactions in 2-phosphorus substituted 1,3-diheteroanes. Thus, in addition to the above mentioned 1,3-dithianes we became interested also in the conformation of 1,3-dioxanes, 1,3-oxathianes and 1,3-diselenanes containing various organophosphorus substituents at the anomeric carbon atom in these heterocyclic rings, as shown below.

The preliminary results obtained till 1987 were the subject of a short

Scheme 1.





$$\text{Ⓟ} = \overset{\text{O}}{\overset{\|}{\text{P}}}(\text{OR}^1)_2 \quad \text{R}^1\text{=Me, Et, CF}_3\text{CH}_2$$

$$\overset{\text{Z}}{\overset{\|}{\text{P}}}\text{R}^1\text{R}^2 \quad \text{Z=O, S, Se} \quad \text{R}^1\text{=R}^2\text{=OR}^1\text{, R}^1\text{=R}^2\text{=Ph}$$

$$\overset{\cdot\cdot}{\text{P}}\text{R}^1\text{R}^2 \quad \text{R}^1\text{, R}^2\text{=Me, Ph}$$

$$\overset{+}{\text{P}}\text{(SMe)Ph}_2 \quad \overset{+}{\text{P}}\text{(SMe)PhMe} \quad \overset{+}{\text{P}}\text{(SMe)Me}_2$$

$$\overset{+}{\text{P}}\text{Ph}_3 \quad \overset{+}{\text{P}}\text{Ph}_2\text{Me} \quad \overset{+}{\text{P}}\text{PhMe}_2 \quad \overset{+}{\text{P}}\text{Me}_3$$

summary account.[17] In this review the actual status of our studies on the anomeric effect in 1,3-diheteroanes is presented.

SYNTHESIS OF MODEL COMPOUNDS

Prior to discussion of the conformational preferences of various organophosphorus substituents in 1,3-diheteroanes it seems desirable to describe briefly synthetic approaches to basic classes of model compounds used in our conformational studies.

Thus, the conformationally labile 2-diphenylphosphinoyl-1,3-dioxanes **5** and **6** were obtained by the Arbuzov reaction of isopropyl diphenylphosphinite with the appropriate trimethyl-2-(1,3-dioxanyl)ammonium iodides.[18] The same reaction was also applied for the synthesis of the diastereoisomeric *cis*- and *trans*-1,3-dioxanes **7** and **8**. Another approach to the diastereoisomeric mixtures of **7** and **8** involved the acid-catalysed transacetalization between an appropriate diol and diphenyl(diethoxymethyl)phosphine oxide. Whereas the Arbuzov reaction afforded more thermodynamically stable isomers of **7** and **8** in greater amounts, the latter approach resulted in the formation of the less thermodynamically stable isomers of **7** and **8** as major products. The pure diastereoisomers of **7** and **8** were separated by column chromatography. Of interest is that according to NMR spectra the *t*-butyl group in *cis*-**7** is almost completely axial.

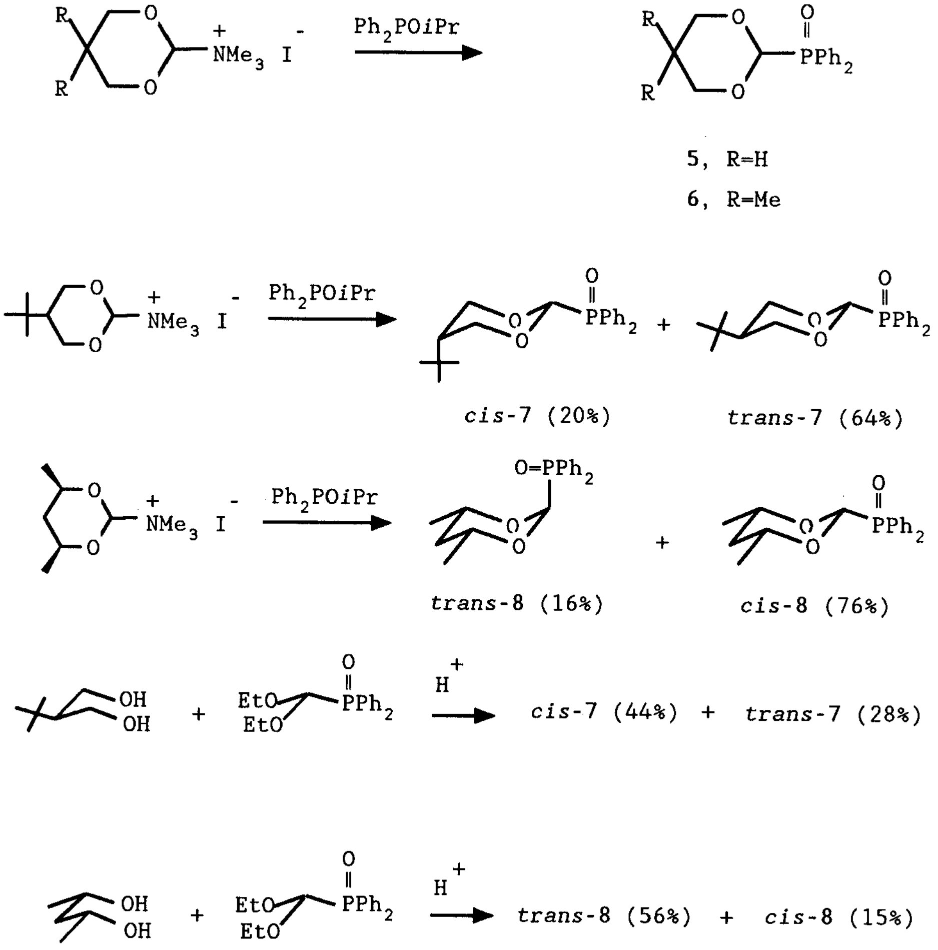
The Arbuzov reaction was also found suitable for the preparation of 2-dimethoxyphosphoryl- or 2-diphenylphosphinoyl-1,3-oxathianes **9-11**, although they were formed in low to moderate yields.

The majority of 2-phosphoryl-1,3-dithianes investigated in our laboratory were prepared by the method mentioned earlier which involves the reaction of 2-chloro-1,3-dithianes with trivalent phosphorus compounds. In this way we obtained in good to excellent yields conformationally labile and conformationally fixed 2-phosphoryl-1,3-dithianes shown below.[21,22] As in the case of diastereomeric 2-phosphoryl-1,3-dioxanes, the Arbuzov reaction afforded a separable mixture of both diastereomers in which the more thermodynamically stable isomer was predominating.

It is interesting to note that a mixture of the diastereomeric dithianes **15** is formed when 4-*t*-butyl-1,2-dithiolane is reacted with dimethyl diazomethanephosphonate.[23] However, this reaction was found to afford the less thermodynamically stable *trans*-**15** as a major isomer (*cis*/*trans* ratio 1:2).

Thiophosphoryl analogues of the phosphine oxides **18** and **19** were easily prepared from the latter upon treatment with phosphorus pentasulfide.[21] The P=O→P=S conversion was found to occur without epimerization at the

Scheme 2



5, R=H

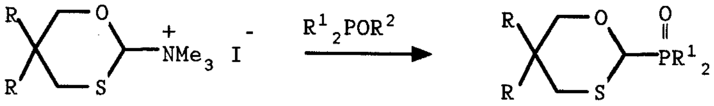
6, R=Me

cis-7 (20%) *trans*-7 (64%)

trans-8 (16%) *cis*-8 (76%)

cis-7 (44%) + *trans*-7 (28%)

trans-8 (56%) + *cis*-8 (15%)

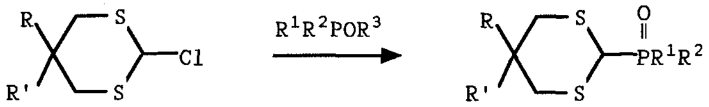


(4)

9, R=H, R^1=MeO

10, R=Me, R^1=MeO

11, R=Me, R^1=Ph



(5)

12, R=R'=Me, $R^1=R^2=MeO$

13, R=R'=Me, $R^1=R^2=EtO$

14, R=R'=Me, $R^1=R^2=CF_3CH_2O$

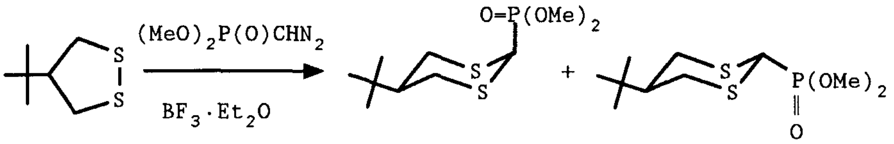
15, R=*t*Bu, R'=H, $R^1=R^2=MeO$

16, R=*t*Bu, R'=H, $R^1=R^2=EtO$

17, R=*t*Bu, R'=H, $R^1=R^2=CF_3CH_2O$

18, R=R'=Me, $R^1=R^2=Ph$

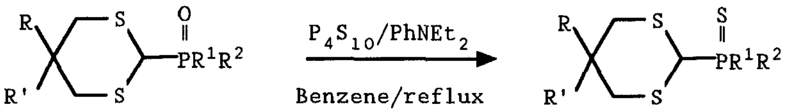
19, R=*t*Bu, R'=H, $R^1=R^2=Ph$



(6)

cis-15 *trans*-15

anomeric carbon atom when pure *cis* or *trans* diastereomers were used as substrates.



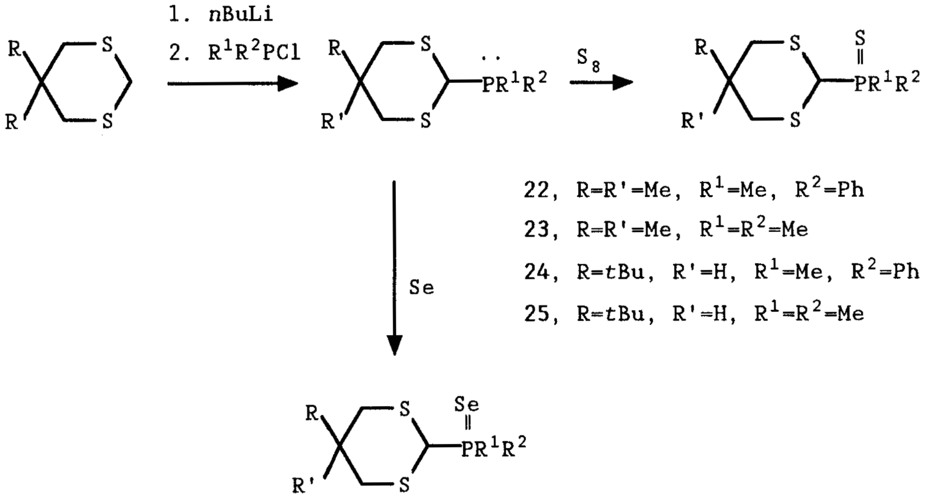
(7)

18 20, R=R'=Me

19 21, R=tBu, R'=H

Since other phosphine oxides were not available by the Arbuzov reaction, the synthesis of the phosphine sulfides **22-25** was accomplished following the two-step procedure of Juaristi *et.al.*[24] At first, the appropriate 2-lithio-1,3-dithianes were treated with chlorophosphines to give 2-phosphino-1,3-dithianes which upon addition of elemental sulfur gave the desired phosphine sulfides. The use of selenium instead of sulfur led to the corresponding phosphine selenides **26** and **27**. In the case of 5-*t*-butyl-1,3-dithiane the first reaction affords the corresponding phosphines in which the phosphino substituent is equatorial. Therefore, the addition of sulfur results in the formation of the corresponding phosphine sulfides with the equatorial thiophosphoryl group. In order to convert *all*-equatorial sulfides **24** and **25** into their epimers, the deprotonation-protonation sequence was applied as shown in equation 9.

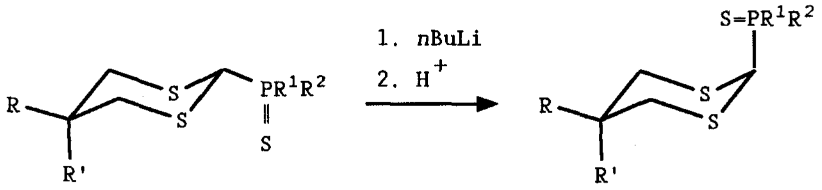
Scheme 3



22, $R=R'=Me$, $R^1=Me$, $R^2=Ph$
23, $R=R'=Me$, $R^1=R^2=Me$
24, $R=tBu$, $R'=H$, $R^1=Me$, $R^2=Ph$
25, $R=tBu$, $R'=H$, $R^1=R^2=Me$

26, $R=R'=Me$, $R^1=R^2=Ph$
27, $R=tBu$, $R'=H$, $R^1=R^2=Ph$

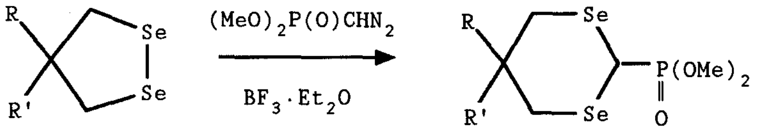
Since 2-dimethoxyphosphoryl-5-*t*-butyl-1,3-dithiane **15** was prepared *via* the insertion of the $(MeO)_2P(O)CH$: moiety into the disulfide bond, we applied[25] the same method (eq.9) for the synthesis of 2-dimethoxy-



(8)

trans-24 *cis*-24
trans-25 *cis*-25

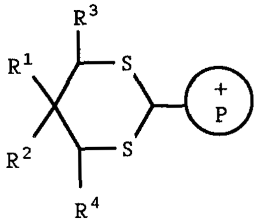
phosphoryl-substituted 1,3-diselenanes **28** and **29** which are the first members of a new class of 1,3-diselenanes containing organophosphorus substituent. Although the conformationally labile **28** as well as a mixture of *cis*- and *trans*-**29** were obtained in low chemical yields, it was possible to carry out complete spectroscopic and structural studies.



(9)

28, R=R'=Me
29, R=tBu, R'=H

In extension of our studies on 1,3-dithianes containing P(O), P(S) and P(Se) groups bonded to the anomeric carbon atom we obtained various 1,3-dithianes with phosphonium groups at C(2). We focused our attention on this class of compounds due to their close relation to ammonium-substituted heteroanes which have been claimed to exhibit the reverse anomeric effect. In the course of our studies we prepared 28 2-phosphonio-substituted 1,3-dithianes[21,26,27] of a general formula **30** essentially by two methods. The first involves the reaction of 2-chloro-1,3-dithianes with tertiary phosphines. The second method is



30

- shown in Scheme 1

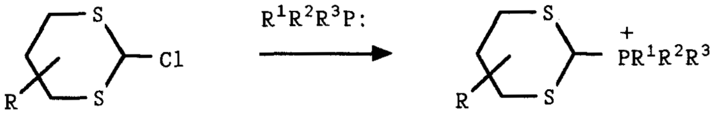
$R^1=R^2=R^3=R^4=H$

$R^1=R^2=Me$, $R^3=R^4=H$

$R^1=tBu$, $R^2=R^3=R^4=H$

$R^1=R^2=H$, $R^3=R^4=Me$

based on methylation of 2-thiophosphoryl-1,3-dithianes by methyl triflate and leads to the corresponding 2-methylthiophosphonio-substituted 1,3-dithianes.



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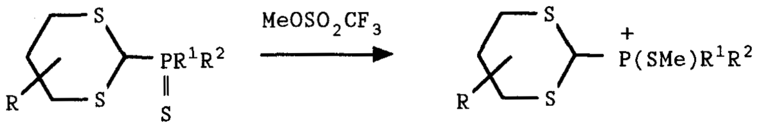


(11)

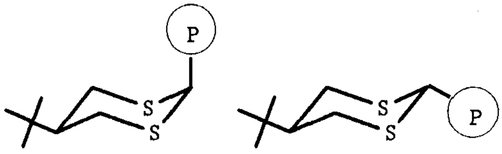
CONFORMATIONAL STUDIES OF 2-PHOSPHORYL-, 2-THIOPHOSPHORYL- AND 2-SELENOPHOSPHORYL 1,3-DIHETEROANES

Configuration and Conformation of 2-P-Substituted 1,3-Diheteroanes

Proton, carbon and phosphorus NMR spectroscopy, X-ray crystallography and chemical correlations were applied to establish the geometry and conformation of the compounds under investigation. Combination of these methods allowed in the first instance to assign unambiguously an axial or equatorial position of the organophosphorus substituent at C(2) in the pure *cis* and *trans* diastereomers of 2-phosphoryl-1,3-dioxanes **7** and **8**, 2-phosphoryl-1,3-dithianes **15**, **16**, **17** and **19** and their thiophosphoryl (**21** and **24**) and selenophosphoryl (**27**) analogues as well as 2-phosphoryl-1,3-diselenane **29**. The heterocyclic rings were found to adopt a chair or slightly distorted chair conformation.

A careful analysis of the collected NMR spectral data revealed that there is a clear relationship between the configuration of the anomeric carbon atom and many spectral parameters. Among them the values of γ-effect and $^3J_{C-P}$ coupling constant in ^{13}C NMR spectra deserve special attention because they may be used for a fast, qualitative and quantitative assessment of a predominant solution conformation of the conformationally labile 2-P-substituted 1,3-diheteroanes.[21]. Table I summarizes the γ-effect and $^3J_{C-P}$ coupling constant values for five

Table I γ-Effect and $^3J_{C-P}$ coupling constant values in ^{13}C NMR spectra of selected diastereomeric 1,3-dithianes.



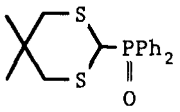
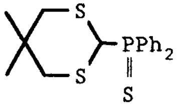
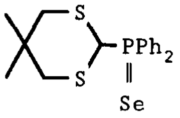
cis *trans*

Compound No	Ⓟ	γ-effect [ppm]	$^3J_{C-P}$ [Hz]	γ-effect [ppm]	$^3J_{C-P}$ [Hz]
15	$P(O)(OMe)_2$	-4.18	0	0.68	8.7
17	$P(O)(OCH_2CF_3)_2$	-4.14	0	-1.04	7.0
19	$P(O)Ph_2$	-3.65	0	1.24	6.5
21	$P(S)Ph_2$	-4.65	0	1.58	7.3
27	$P(Se)Ph_2$	-4.80	0	1.70	7.2

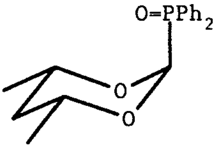
pairs of diastereomeric 2-P-substituted 5-*t*-butyl-1,3-dithianes.

It is clearly seen from Table I that in the case of *cis*-isomers with the axial phosphorus substituent at C(2) γ-effect is negative and amounts some ppm while the coupling constant between P and C(4) and C(6) observed in these compounds is zero. When the phosphoryl, thiophosphoryl or selenophosphoryl groups are located in the equatorial position (*trans*-isomers) the γ-effect values are positive or nearing to zero and the coupling constants $^3J_{C-P}$ are about 7-9 Hz.

Based on this rather clear dependence one may suppose that the conformationally labile compounds **20** and **26**, which contain diphenylthiophosphinoyl and diphenylselenophosphinoyl group at C(2), 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. On the other hand, the 1,3-dithiane **18** should exist predominantly as axial conformer.

No		γ-effect [ppm]	$^3J_{C-P}$ [Hz]
18		-2.94	0
20		-1.57	3.4
26		-1.16	3.7

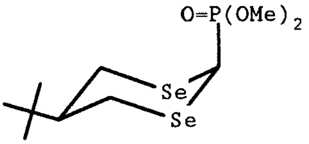
The same relationship between the configuration at C(2) and the γ-effect and $^3J_{C-P}$ values has been found for the diastereomeric 1,3-dioxanes[18,19] and 1,3-diselenanes[25] as shown below. Based on this



trans-8

γ-effect = -3.60 ppm

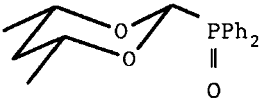
$^3J_{C-P}$ = 2.4 Hz



cis-29

γ-effect = -1.32 ppm

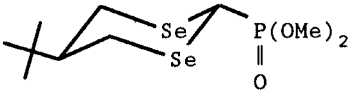
$^3J_{C-P}$ = 0 Hz



cis-8

γ-effect = 1.86 ppm

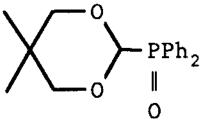
$^3J_{C-P}$ = 10.4 Hz



trans-29

γ-effect = 1.73 ppm

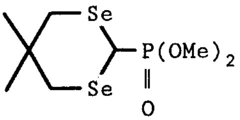
$^3J_{C-P}$ = 4.5 Hz



6

γ-effect = -0.72 ppm

$^3J_{C-P}$ = 10.4 Hz



28

γ-effect = -0.60 ppm

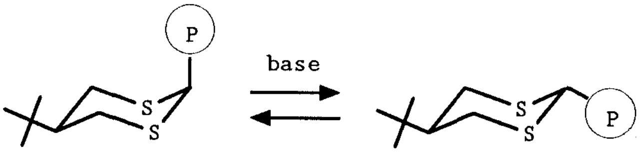
$^3J_{C-P}$ = 0 Hz

data it is reasonably to assume that the diphenylphosphinoyl group in the 5,5-dimethyl-1,3-dioxane **6** strongly prefers the equatorial position while the dimethoxyphosphoryl group in 5,5-dimethyl-1,3-diselenane **28** should be axial.

Quantification of the Conformational Preferences and Anomeric Effect in 2-P-Substituted 1,3-Diheteroanes

The preference of a given substituent for axial or equatorial position can be determined by equilibration of diastereomeric compounds. In contrast to the *cis*- and *trans*-dioxanes **7** and **8**, where all attempts to equilibrate them under basic or acidic conditions failed, the equilibration of 1,3-dithiane derivatives was found to occur smoothly in the presence of sodium methoxide or tertiary amines. The ratio of the diastereomers was determined either as the ratio of integrals in ^1H NMR spectra or as the ratio of the appropriate signals in ^{31}P NMR spectra. It should be noted that since the ^{31}P spin-lattice relaxation times[28] of diastereomers are very similar, the ratio of integrals in ^{31}P NMR spectrum can be treated as a quantitative measure of the relative amounts of isomers. Table II summarizes the equilibrium

Table II Equilibrium constants K and free energy differences ΔG° for some 2-P-substituted 5-*t*-butyl-1,3-dithianes.



Compound No	Ⓟ	K_{exp}	ΔG°_{exp} [kJ/mol]
15	$P(O)(OMe)_2$	0.168	4.35±0.12
16	$P(O)(OEt)_2$	0.142	4.76±0.28
19	$P(O)Ph_2$	0.187	4.09±0.25
21	$P(S)Ph_2$	0.425	2.08±0.17
24	P(S)MePh	0.345	2.59±0.13
25	$P(S)Me_2$	0.593	1.27±0.15
27	$P(Se)Ph_2$	0.499	1.69±0.14

constants and the related ΔG° values for some selected 5-*t*-butyl-1,3-dithianes.

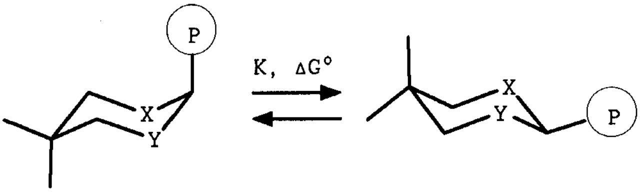
To quantify the conformational effects operative in conformationally mobile 1,3-diheteroanes the Eliel's approach (Eq's 12)[29] was applied

$$I_{obs} = x \cdot I_{ax} + (1-x) \cdot I_{eq} \qquad (12)$$

$$K = \frac{1-x}{x} \qquad \Delta G^{\circ} = -RT \ln K$$

assuming that the value of the γ-effect or $^{3}J_{C-P}$ in the mobile diheteroane is the weighted average of those for the conformationally fixed model axial and equatorial diastereomers. The results obtained by this method are collected in Table III.

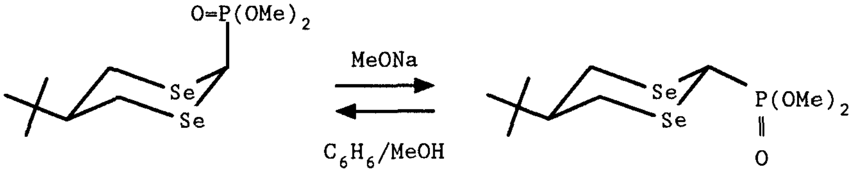
Table III Calculated equilibrium constants K and free energy differences ΔG° for some 2-P-substituted 5,5-dimethyl-1,3-diheteroanes.



Compound No	Ⓟ	K_{cal}	ΔG°_{cal} [kJ/mol]
6, X=Y=O	$P(O)Ph_2$	14.2	-6.5
11, X=O, Y=S	$P(O)Ph_2$	2.7	-2.4
18, X=Y=S	$P(O)Ph_2$	0.17	4.4

The results presented above clearly show that the phosphoryl group in the 1,3-dioxane **6** and 1,3-oxathiane **11** prefers the equatorial position at C(2) what is in a sharp contrast with the situation observed for the 1,3-dithiane **18**.

The equilibration of the diastereomeric 1,3-diselenanes **29** (Eq.13) as well as calculation of the equilibrium constant (Eq.14) for the conformationally mobile diselenane **28** *via* the weighted average method (using the γ-effect values for individual conformers of **28** taken from the low-temperature (180K) ^{13}C NMR spectra) provided quantitative data supporting the axial preference of the dimethoxyphosphoryl group in the 1,3-diselenane ring.[25]

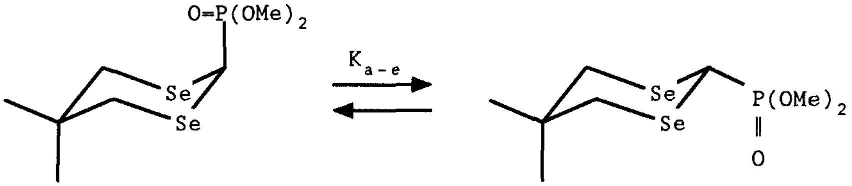


(13)

cis-29 *trans*-29

K = 0.115±0.06

ΔG° = 5.27±0.12 kJ/mol



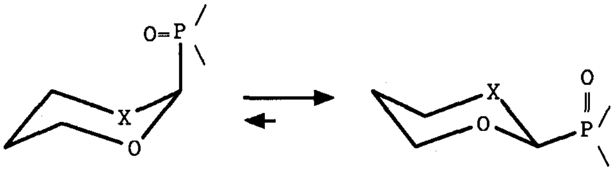
(14)

ax-28 K = 0.325 eq-28

ΔG° = 2.77 kJ/mol

The quantitative and qualitative data on the conformational preferences in 2-organophosphorus-substituted 1,3-diheteroanes presented above lead to the following general conclusions:

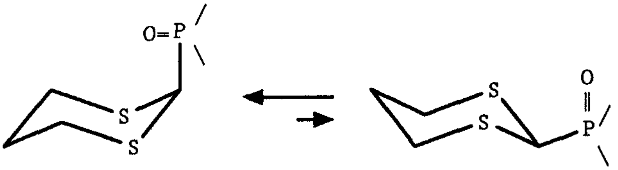
a) in 1,3-dioxanes and 1,3-oxathianes containing phosphoryl group at the anomeric carbon atom C(2) conformational equilibrium is strongly shifted towards the equatorial conformer.



(15)

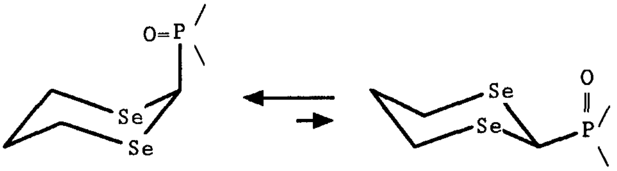
X=O, S

b) on the contrary, the phosphoryl group at C(2) in 1,3-dithianes shows a strong preference for the axial position.



(16)

c) 2-phosphoryl-1,3-diselenanes exist preferentially as axial conformers resembling conformational behaviour of 1,3-dithianes.



(17)

In this context, it is interesting to point out that molecular mechanics calculations[30] of the conformational behaviour of 2-phosphoryl-1,3-dioxane, 2-phosphoryl-1,3-dithiane and 2-thiophosphoryl-1,3-dithiane are fully consistent with the experimental observations and data so far collected. The energy of the axial and equatorial conformations of the above mentioned heteroanes was calculated according to Equation 18.

$$E = E_{nb} + E_{t} + E_{ad} + E_{lep} \qquad (18)$$

where E_{nb} - energy of nonbonding interactions

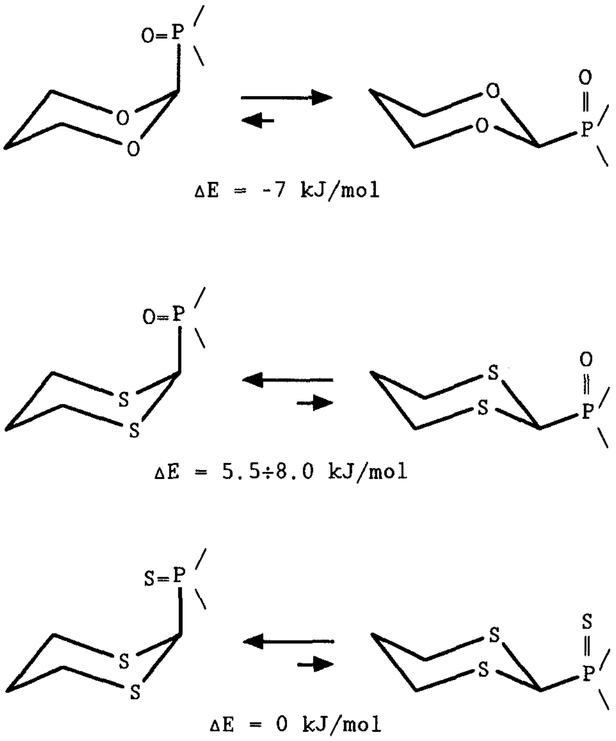
E_t - torsional energy

E_{ad} - energy of angle deformations

E_{lep}- energy of lone electron pair interactions

The calculated energy differences between the axial and equatorial conformations, ΔE, are shown in Scheme 4. According to MM-calculations

Scheme 4



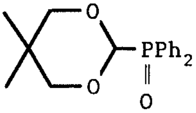
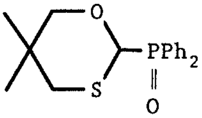
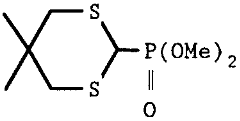
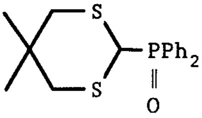
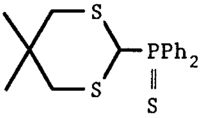
the axial chair conformer in 1,3-dioxane is destabilized by 1,3-*syn*-axial interactions between the 4,6-methylene groups and the bulky phosphoryl group. These steric interactions are stronger than the anomeric effect operating in this system. By contrast, the equatorial chair conformation of 2-phosphoryl-1,3-dithiane is less stable than the axial one due to repulsive interactions between the lone electron pairs on sulfur and phosphoryl oxygen.

Finally, the magnitude of the anomeric effect operating in the diheteroanes under discussion was estimated according to the Franck's methodology (Eq.19)[31] using the ΔG^{o}_{C} values taken from the

$$\Delta G^{o}_{AE} = \Delta G^{o}_{H} - F \cdot \Delta G^{o}_{C} \qquad (19)$$

literature.[24,32,33] The values of the calculated anomeric effect are given in Table IV. They are similar to those obtained by Juaristi and

Table IV Anomeric effect values in selected 2-phosphoryl and 2-thiophosphoryl 1,3-diheteroanes.

Compound No	Structure	ΔG^{o}_{AE} [kJ/mol]
6		19.7
11		19.0
12		15.1
18		14.3
20		11.6

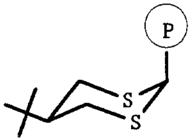
coworkers in their independent studies.[34]

NATURE OF THE ANOMERIC EFFECT IN LIGHT OF CRYSTALLOGRAPHIC AND SPECTRAL DATA.

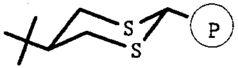
A commonly accepted interpretation of the anomeric effect operating in heteroanes is based on interactions between a lone pair of electrons centered on a ring heteroatom and the adjacent vacant antibonding orbital (σ^*) associated with the exocyclic carbon-heteroatom bond.[11] In the axial conformer of a heteroane the orbital bearing the lone pair is antiperiplanar to the exocyclic carbon-heteroatom bond what allows donation of electrons from the lone pair into the antibonding orbital of this bond. In the equatorial conformer of a heteroane these two orbitals are orthogonal and do not overlap. Therefore, the anomeric effect is due to stabilization of the axial conformation by a fovourable stereoelectronic interaction. Such a stereoelectronic interpretation of the anomeric effect implies that the endocyclic heteroatom-carbon bond should be shortened whereas the exocyclic carbon-heteroatom bond should be elongated. However, as mentioned above preliminary X-ray data on 2-phosphoryl-substituted 1,3-dithianes **1** and **4** and 2-phosphoryl-1,3,5-trithiane **2** revealed that the expected changes in bond lengths i.e. the shortening of the C-S bond and lengthening of the C-P bond are not observed. Therefore, the role of the $n_S-\sigma^*_{C-P}$ negative hyperconjugation as a sole or principle source of the anomeric effect operating in 2-phosphoryl-substituted 1,3-diheteroanes was questioned.

Having in our hands a large number of the diastereomerically pure *cis*- and *trans*-2-P-substituted 1,3-diheteroanes we decided to determine their solid state structures[35] with the hope to get better comparative

Table V Selected bond distances in diastereomeric 2-P-substituted 5-*t*-butyl-1,3-dithianes.



cis

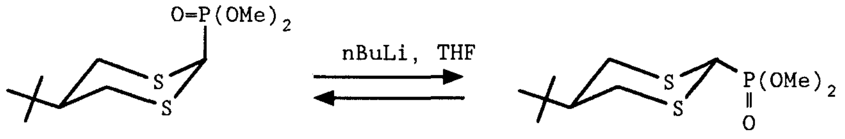


trans

Compound		C(2)-P	C(2)-S		C(2)-P	C(2)-S	
No	Ⓟ	[Å]	[Å]	[Å]	[Å]	[Å]	[Å]
15	$P(O)(OMe)_2$	1.782(5)	1.811(6);	1.812(5)	1.798(4)	1.796(4);	1.791(5)
17	$P(O)(OCH_2CF_3)_2$	1.794(3)	1.796(4);	1.814(4)	1.794(3)	1.806(3);	1.815(3)
19	$P(O)Ph_2$	1.834(4)	1.805(5);	1.803(5)	1.821(2)	1.807(3);	1.799(2)
21	$P(S)Ph_2$	1.817(5)	1.803(4);	1.817(5)	1.831(3)	1.809(4);	1.814(5)
27	$P(Se)Ph_2$	1.855(4)	1.801(5);	1.807(5)	1.841(3)	1.804(3);	1.810(3)

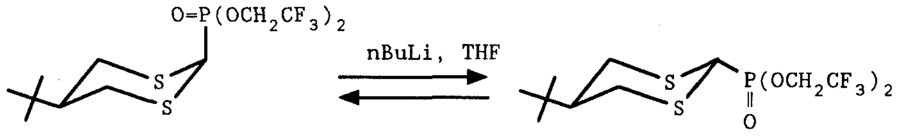
data. The selected bond lengths in *cis*- and *trans*-2-phosphoryl-, 2-thiophosphoryl- and 2-selenophosphoryl-5-*t*-butyl-1,3-dithianes are collected in Table V.

An inspection of the X-ray data in Table V reveals that the C(2)-P bond lengths in diastereomers are not characteristic for the position of phosphorus. More interestingly, in the equatorial isomers of **15** and **21** these bonds are longer than those in the axial ones. On the other hand, in *cis*-**19** and *cis*-**27** with the axial P-substituent they are shorter in agreement with the concept of the n_S-σ^*_{C-P} negative hyperconjugation. In **17** the axial C(2)-P bond is of the same length as the equatorial one. Similarly, the endocyclic C(2)-S bond lengths practically do not depend on configuration at the anomeric carbon atom. However, comparison of the structural data between *cis*-**15** and *cis*-**17** is of interest. In the latter compound containing the strongly electron-withdrawing $(CF_3CH_2)_2P(O)$ group one observes a rather distinct



(20)

ΔG^o_{293}=6.66±0.66 kJ/mol

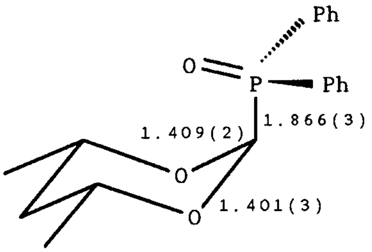


(21)

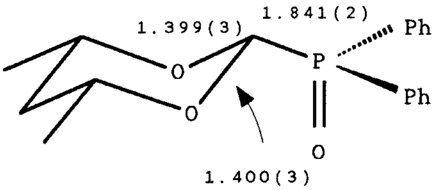
ΔG^o_{293}=11.06±0.60 kJ/mol

difference between two C(2)-S bond distances of 0.018Å while in *cis*-**15** they are equal. If one also takes into account that ΔG° value for **15** is *ca* 3 kJ/mol smaller than that for **17**, it is reasonable to assume that the anomeric effect in 1,3-dithianes is due at least in part to the stereoelectronic interactions discussed above.

In contrast to 1,3-dithianes, crystallographic data[19] for *cis*- and *trans*-1,3-dioxanes **8** (see below) provide more convincing arguments for the stereoelectronic nature of the anomeric effect operating in this system. First of all, it should be pointed out that a significant elongation of the axial C(2)-P bond (by 0.025Å), which can be expected on the basis of the negative hyperconjugation, is observed. Moreover, while in *cis*-**8** both C(2)-O bond lengths are equal, they differ by 0.008Å in *trans*-**8**. The negative hyperconjugation usually results in the decrease of the one-bond coupling constant through the acceptor bond in the NMR spectra of molecules exhibiting anomeric effect.[36-38] In accord with this, the coupling constant $^1J_{C-P}$ for *trans*-**8** is smaller than that for *cis*-**8**.



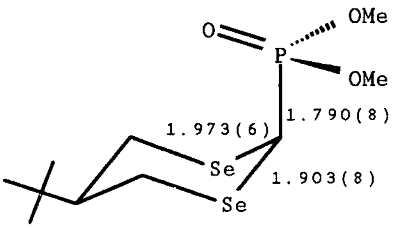
trans-8



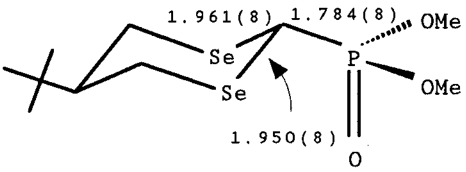
cis-8

$^1J_{C-P}$	[Hz]	94.3	118.8
$\nu_{P=O}$	[cm^{-1}]	1188	1196

In the case of *cis*-2-dimethoxyphosphoryl-5-*t*-butyl-1,3-diselenane (*cis*-**29**) the difference between both C(2)-Se bond lengths is very pronounced (0.07Å) and the shortest selenium-carbon bond in this isomer is *ca* 0.05Å shorter than two C(2)-Se bond distances in *trans*-**29** which are almost equal. Though the C(2)-P bond lengths are close in *cis*- and *trans*-**29**, the difference in carbon-selenium distances is large enough to take the n_{Se}-σ^*_{C-P} interaction into account as responsible for the shortening of this bond in *cis*-**29** and for the anomeric effect observed in this system.[25]



cis-29

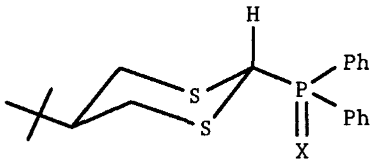


trans-29

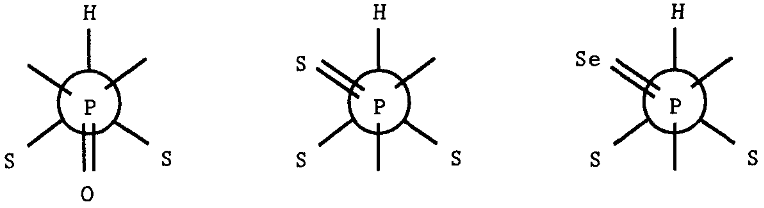
In summary, analysis of the structural parameters in 2-P-substituted 1,3-diheteroanes suggests that the negative hyperconjugation may be considered as one of the factors responsible for the anomeric effect. Even in the case of 2-P-substituted 1,3-dithianes one can not exclude the n_S-σ^*_{C-P} overlap because the lack of the expected bond length changes may result from a combination of several other, microscopic factors.

Among them, repulsive interactions between the lone electron pairs on the endocyclic sulfur and P=X heteroatom (X=O, S, Se) should be taken into account. This type of interactions, suggested by molecular mechanics calculations[30], destabilizes the equatorial position of the $R_2P(X)$ group and enhances the anomeric effect. Since repulsive interactions are known to be accompanied by bond lengthening, the C(2)-P bond should reflect operation of this effect. Indeed, the equatorial C(2)-P bond length in 1,3-dithianes increases on going from the phosphoryl to thiophosphoryl and to selenophosphoryl group (see Scheme 5).

Scheme 5



	C(2)-P [Å]
19, X=O	1.821 (2)
21, X=S	1.831 (3)
27, X=Se	1.841 (3)

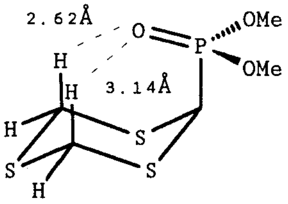


19 21 27

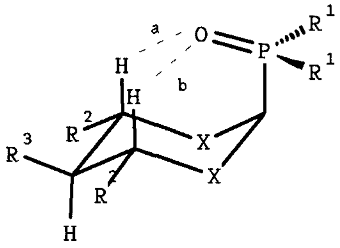
In addition to elongation of the C(2)-P bond, the n_S-n_X repulsions have influence on the conformation around this bond. Thus, while in the dithiane **19** the phosphoryl oxygen atom is located in the solid state between two endocyclic sulfur atoms (H-C-P=O angle equal to 170.4°), in thiophosphoryl and selenophosphoryl analogues **21** and **27** one observes the gauche orientation of sulfur and selenium in respect to hydrogen at C(2). This finding is consistent with the increasing n_S-n_X repulsive interactions on going from P=O to P=S and to P=Se.

Our X-ray analysis of 2-dimethoxyphosphoryl-1,3,5-trithiane (**2**) published in 1984[14] showed not only that the phosphoryl group is axial but also that its oxygen is almost symmetrically situated above the 1,3,5-trithiane ring and 2.62 and 3.14Å away from the axial hydrogens at C(4) and C(6). Such a situation has been found to be general for other axial 2-phosphoryl-1,3-diheteroanes as shown below (Scheme 6). In view of the available literature data on the C-H···O hydrogen bond in crystals[39,40] it is quite reasonable to assume the formation in all

Scheme 6



2

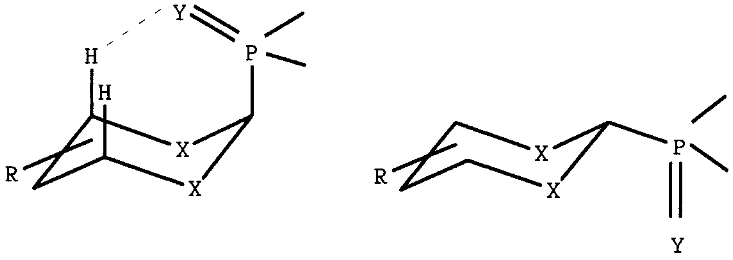


8,	X=O,	R^1=Ph,	R^2=Me,	R^3=H	a=2.40Å,	b=2.53Å
15,	X=S,	R^1=OMe,	R^2=H,	R^3=*t*Bu	a=2.49Å,	b=2.57Å
31,	X=S,	R^1=OMe,	R^2=Me,	R^3=H	a=2.54Å,	b=2.66Å
19,	X=S,	R^1=Ph,	R^2=H,	R^3=*t*Bu	a=2.54Å,	b=2.76Å
29,	X=Se,	R^1=OMe,	R^2=H,	R^3=*t*Bu	a=2.55Å,	b=2.63Å

these structures of a weak intramolecular hydrogen bond between phosphoryl oxygen and at least one axial hydrogen. This effect may additionally stabilize the axial conformation of 2-phosphoryl-substituted 1,3-diheteroanes.

Crystallographic and spectroscopic data imply also that other hyperconjugative interactions such as $\sigma_{C(4,6)-S}-\sigma^*_{C(2)-P}$ and $\sigma_{C(4,6)-S}-\pi^*_{P=Y}$ may be operative in 1,3-diheteroanes under investigation. The first of them should stabilize the equatorial position of the organophosphorus substituent at C(2) while the second is expected to stabilize the axial one. Therefore, combination of all the stabilizing and destabilizing effects depicted schematically below (Scheme 7) determines the conformational preference of P-substituents in 1,3-diheteroanes.

Scheme 7



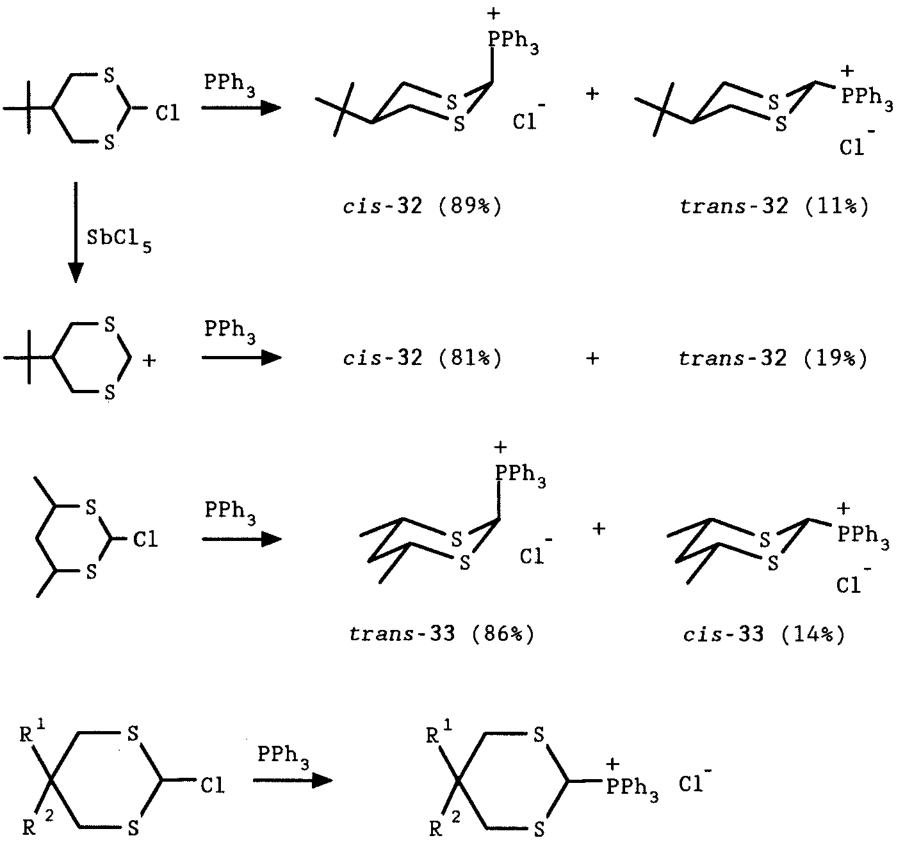
Stabilizing effect	n_X-σ^*_{C-P} H···Y=P $\sigma_{C(4,6)-S}$-$\pi^*_{P=Y}$	$\sigma_{C(4,6)}$-σ^*_{C-P}
Destabilizing effect	1,3-*syn*-diaxial	n_X-n_Y

CONFORMATIONAL BEHAVIOUR OF 2-PHOSPHONIO-1,3-DITHIANES.

In the course of our studies on the anomeric effect in 1,3-diheteroanes we became interested also in the conformation of 1,3-dithianes bearing phosphonium substituents at the anomeric carbon atom. Investigation of the conformational behaviour of this class of compounds was stimulated by the fact that the ammonium groups at the anomeric carbon center prefer to be equatorial.[41,42] The latter case represents an example of the "reverse anomeric effect"[43] and may be better explained in terms of dipolar interactions. Therefore, it was expected that the reverse anomeric effect may be operative in a similar S-C-P$^+$ system with the positively charged phosphorus atom.

In the first stage of our work,[26] the conformationally fixed and mobile 2-triphenylphosphonio-1,3-dithianes were prepared by treatment of the appropriate 2-chloro-1,3-dithianes with triphenylphosphine as shown in

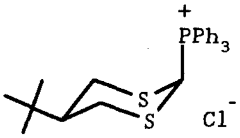
Scheme 8



34, $R^1=R^2=H$ (89%)
35, $R^1=R^2=Me$ (72%)

Scheme 8. X-Ray analysis of the major product obtained in the reaction of 2-chloro-5-*t*-butyl-1,3-dithiane with triphenylphosphine revealed that it has the *cis*-geometry with the axial triphenylphosphonium group. Furthermore, *cis*-**32** as well as *trans*-**33** were found, by means of the equilibration experiments, to be the kinetically controlled products whereas *trans*-**32** and *cis*-**33** with the equatorial $^+PPh_3$ group are thermodynamically more stable isomers.

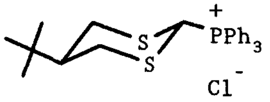
Analysis of ^1H, ^{13}C and ^{31}P NMR spectra of the phosphonium salts prepared as above showed that, among many spectral parameters which may be used to assign the geometry of the ring in these salts, the γ-effect and $^3J_{C-P}$ coupling constant values in ^{13}C NMR spectra are the most conclusive (see below). Thus, the γ-effect value is negative and amounts -3÷-4 ppm for all 1,3-dithianes with triphenylphosphonium group located axially. When this group is equatorial the γ-effect is positive of about 1÷2 ppm. The $^3J_{C-P}$ coupling constant values are zero and 7÷8 Hz, respectively.



cis-32

γ-effect = -4.48 ppm

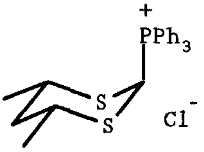
$^3J_{C-P}$ = 0 Hz



trans-32

γ-effect = 1.09 ppm

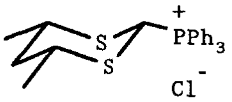
$^3J_{C-P}$ = 7.5 Hz



trans-33

γ-effect = -3.55 ppm

$^3J_{C-P}$ = 0 Hz



cis-33

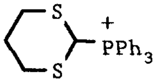
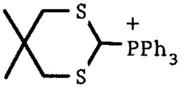
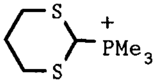
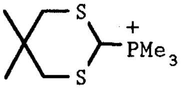
γ-effect = 1.14 ppm

$^3J_{C-P}$ = 7.4 Hz

The corresponding data for the conformationally labile triphenylphosphonium salts **34** and **35** and their trimethyl-analogues **36** and **37** summarized in Table VI suggest that the conformational equilibrium is shifted here towards the equatorial conformers.

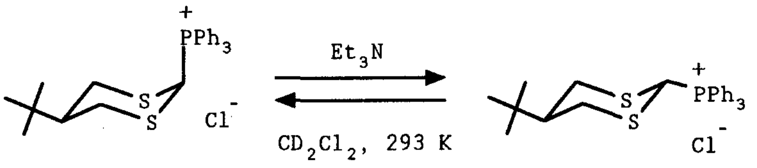
More precise data on the conformatioanal equilibrium in 2-triphenylphosphonio-1,3-dithianes were obtained from the base-catalyzed

Table VI γ-Effect and $^3J_{C-P}$ coupling constant values for some 2-phosphonio-1,3-dithianes.

No	Compound Structure	γ-effect [ppm]	$^3J_{C-P}$ [Hz]
34		0.11	4.9
35		-0.27	5.7
36		-1.03	4.8
37		-1.08	5.4

equilibration of the diastereomeric salts *cis*- and *trans*-**32** and **33**. The equilibrium constants K and ΔG° values determined in this way are shown below. Assuming that the γ-effect value in the conformationally mobile 1,3-dithianes **34** and **35** is the weighted average of those for the model diastereomers *cis*- and *trans*-**32** or *trans*- and *cis*-**33** it was possible to calculate the equilibrium constant and ΔG° values for the mobile systems (see equations 22 and 23).

The free energy differences determined experimentally or calculated for 2-triphenylphosphonium-1,3-dithianes point to an equatorial preference of the $^+PPh_3$-group and may be considered to be consistent with the operation of the reverse anomeric effect. However, these values are in our opinion surprisingly small. This observation prompted us[27,44] to prepare wider range of 2-phosphonio-1,3-dithianes and to determine the equilibrium constant K and ΔG° values for them. The results of this set

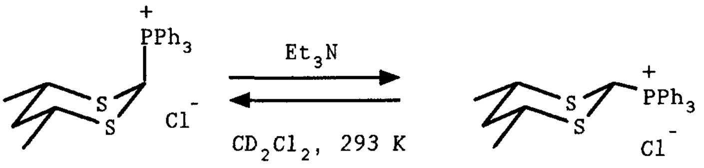


(20)

cis-32 *trans*-32

K = 1.74

$\Delta G^\circ = -1.35$ kJ/mol



(21)

trans-33 *cis*-33

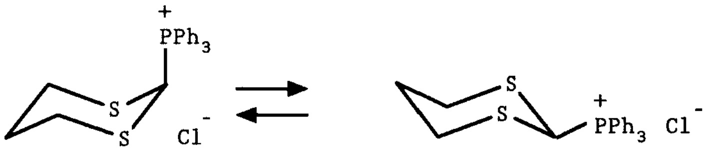
K = 6.10

$\Delta G^\circ = -4.40$ kJ/mol

of experiments are collected in Table VII.

It is clearly seen from the data in Table VII that for the 2-phosphonio-1,3-dithianes **40**, **41**, **42**, **43** and **45** the axial preference predominates ($K<1$, $\Delta G^\circ>0$) indicating unequivocally the operation of the generalized anomeric effect for the $^+PPh_2Me$ and $^+PPhMe_2$ groups attached to the anomeric carbon atom of the 1,3-dithiane ring. Therefore, the conformational preference of the 2-phosphonium substituents in 1,3-dithiane ring most probably depends on the competition between the anomeric effect and steric effect (1,3-*syn*-diaxial interactions) operating in opposite directions.

It should be noted that spectral properties of the 2-phosphonio-1,3-dithianes investigated here support hyperconjugative origin ($n_S-\sigma^*_{C-P}$) of the observed anomeric effect.[44] The second mechanism responsible for the anomeric effect in $S-C-P^+$ system, which could be taken into account, is connected with the destabilizing interactions between lone electron pairs on the endocyclic sulfur atoms and

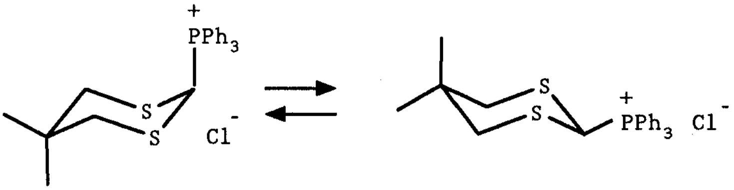


(22)

ax-34 eq-34

K = 4.84, ΔG° = -3.80 kJ/mol (using 32)

K = 3.65, ΔG° = -3.15 kJ/mol (using 33)



(23)

ax-35 eq-35

K = 3.14, ΔG° = -2.80 kJ/mol (using 32)

K = 2.35, ΔG° = -2.10 kJ/mol (using 33)

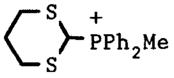
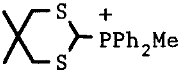
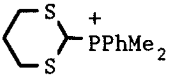
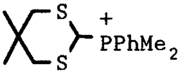
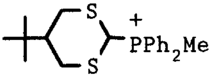
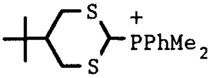
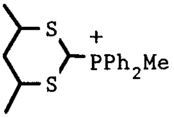
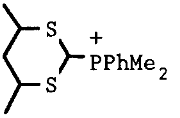
π-electrons of the phenyl ring(s) attached to the equatorial phosphorus.

Finally, it is interesting to mention that some 2-methylthiophosphonium salts **46**, easily obtained by methylation of 2-thiophosphoryl-1,3-dithianes with methyl triflate, undergo fast, spontaneous epimerization.[45] The rate of this process was found to be dependent on the substituents at phosphorus and increases in the following order:

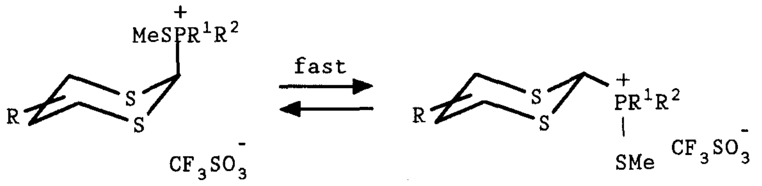
$$0 \cong Me_2P^+SMe_2 < MePhP^+SMe \ll Ph_2P^+SMe$$

A very low kinetic H/D isotope effect at C(2) and cross-experiments with two pairs of variously substituted 2-methylthiophosphonio-1,3-dithianes strongly support a dissociative mechanism of the

Table VII Equilibrium constants K and free energy differences ΔG° for ax⇌eq equilibrium in 2-phosphonio-1,3-dithianes.

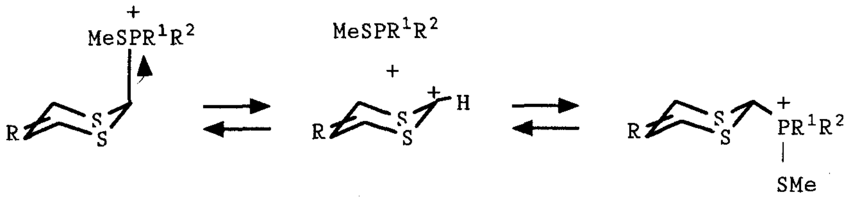
Compound No	Compound Structure	K	ΔG°_{293} [kJ/mol]
38		2.38	-2.13
39		1.57	-1.11
40		0.69	0.91
41		0.52	1.61
42	 *cis, trans*	0.83	0.45
43	 *cis, trans*	0.34	2.63
44	 *cis, trans*	2.12	-1.83
45	 *cis, trans*	0.58	1.33

epimerization under discussion involving the C-P bond breaking (eq.25). This finding is very interesting because a spontaneous, reversible heterolysis of the C-P bond seems, to the best of our knowledge, to be



(24)

46



(25)

unknown.

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