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Second-Row Anomeric Interactions: The Involvement of Phosphorus

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ABSTRACT

*Proton NMR spectroscopy and x-ray crystallographic studies demonstrate the predominance of the axial conformer of 2-(diphenylphosphinoyl)-1,3-dithiane (**1**). Chemical equilibration of anancomeric models (**3** ⇌ **4**) allows quantitative determination of the conformational free energy in **1**, 1.0 kcal/mol, which corresponds to an anomeric effect of 2.64–3.74 kcal/mol, depending on the method used for estimating it. This value indicates that the anomeric effect operative in **1** may be among the largest yet measured.*

Five distinct rationalizations are considered to account for such a strong S-C-P(O) anomeric effect: (a) *dipole-dipole interactions,* (b) *electrostatic, attractive interaction between the phosphoryl oxygen and the syn-axial hydrogens in **1**-axial,* (c) *delocalization of the lone pair on the endocyclic heteroatom into the antiperiplanar (axial) adjacent polar C-P bond,* (d) *through-space 3p-3d electron donation from sulfur to phosphorus, and* (e) *repulsive interaction between the lone pairs on sulfur and on the phosphoryl oxygen. All these hypotheses have some experimental and/or theoretical support, but evidence contrary to expectation can be found also to argue against each one of them.*

*The conformational preference of the diphenylthiophosphinoyl group in the 1,3-dithian-2-yl ring was determined by nuclear magnetic resonance (NMR) analysis and by chemical equilibration of diastereomeric models. The slight predominance of axial 2-(diphenylthiophosphinoyl)-1,3-dithiane (**13**-ax) over **13**-eq reflects nonetheless the influence of a strong S-C-P anomeric interaction, worth ca. 2.3 kcal/mol.*

*Spectroscopic evidence for the predominance of the equatorial conformers in 2-(diphenylphosphinoyl)-1,3-oxathiane (**19**) and 2-(diphenylphosphinoyl)-1,3-dioxane (**22**) was confirmed by the study of derivatives containing counterpoise substituents, or by chemical equilibration on anancomeric models.* $\Delta D^{\circ}_{27^{\circ}C}$ *[P(O)Ph$_2$]= −3.23 kcal/mol was determined for the dioxane (chloroform solution), and* $\Delta G^{\circ}_{55^{\circ}C}$ *[P(O)Ph$_2$]= −1.42 kcal/mol for the oxathiane (ethanolic solution). Nevertheless, evaluation of the different steric requirements in **1**, **13** and **22** reveals that the magnitude of the O-C-P(O) and S-C-P(O) anomeric effects in the heterocycles is, in fact, quite similar, close to kcal/mol.*

DISCOVERY OF THE S-C-P(O) ANOMERIC EFFECT

2-[1,3]Dithianyldiphenylphosphine oxide (**1**) was prepared in our laboratory as a potential precursor of ketene dithioketals [1] (Scheme 1). Treatment of 1,3-dithiane with *n*-butyllithium and chlorodiphenylphosphine, followed by spontaneous oxidation during workup afforded **1** in 40% isolated yield [2, 3].

Assignment of the proton NMR spectrum of **1** indicated a very large (ca. 1.2 ppm) chemical shift difference between axial and equatorial protons at C(4, 6). That the signals at 3.70 and 2.50 ppm correspond to the axial and equatorial protons, respectively, was confirmed by double-irradiation experiments [2]. These spectroscopic observations are evidence for a deshielding effect of a *predominantly axial* phosphoryl group on the syn-axial H(4, 6) (Equation 1).

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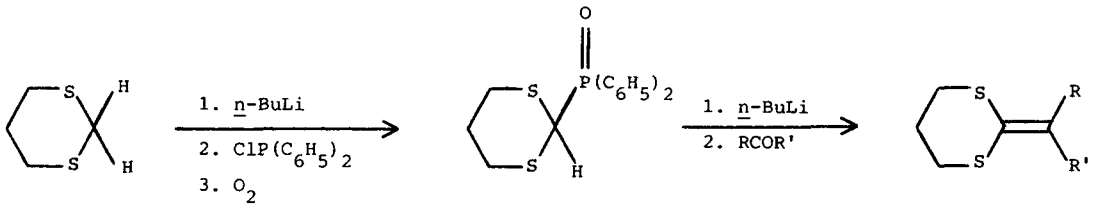
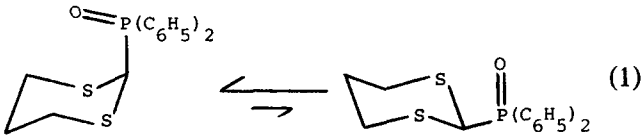


1

SCHEME 1



1-axial **1**-equatorial (1)

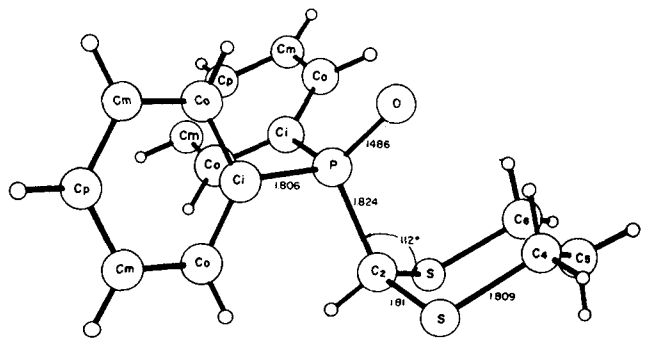
Support for this hypothesis came from the observation that the downfield shift produced by the addition of $Eu(fod)_3$ is in the order H(4, 6 axial) > H(2) > H(4, 6 equatorial) > H(5). Observation of Dreiding models indicates that this result is reasonable only if one assumes the axial orientation for the phosphinoyl group, with the P-O bond above the dithiane ring.

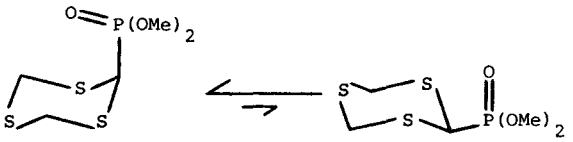
Definitive proof for the conformation of **1** was obtained by single-crystal x-ray diffraction [2]. A perspective view of the molecular structure is shown in Figure 1. The heterocyclic six-membered ring exists in a somewhat flattened chair conformation with the substituent being axial.

There was, therefore, clear evidence for a strong anomeric interaction between the second-row elements sulfur and phosphorus (S-C-P=O). While much work has been dedicated to studies of the anomeric effect involving first-row elements [4–6], this work constituted the first account of a S-C-P anomeric interaction [2, 3].

Soon thereafter, Mikolajczyk et al. [7, 8] reported NMR evidence suggesting that the 2-dimethoxyphosphoryl-1,3,5-trithiane analogue also adopts an axial conformation (Equation 2). An x-ray crystallographic structure of **2**-axial confirmed this [7].

FIGURE 1 Perspective view of the molecular structure of **1**.

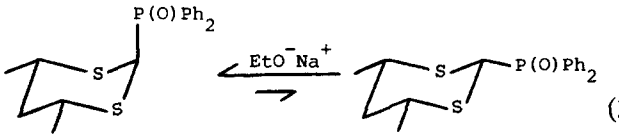




2-axial **2**-equatorial (2)

QUANTIFICATION OF THE AXIAL PREFERENCE OF THE DIPHENYLPHOSPHINOYL GROUP IN 1

To quantify the conformational effect operative in **1**, the conformationally fixed (anancomeric) derivatives **3** and **4** were prepared, and their proton NMR spectra were compared with that of **1** (all three in $CDCl_3$). Most interestingly, the coupling constants of H(2) to phosphorus in **1**, **3**, and **4** vary considerably: 6, 15, and 4.2 Hz, respectively. On the assumption that $^2J_{H(2)/P}$ in the mobile dithiane **1** is the weighted average of those for the model diastereomers **3** and **4**, then $K = (J_{ax} - J)/(J - J_{eq}) = 1/5$, which yields $\Delta G^\circ_{39°C} = 1.0$ kcal/mol for the free energy difference favoring **1**-axial over **1**-equatorial [2] (Equation 3).



3 **4** (3)

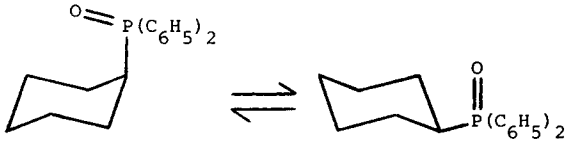
$^2J_{H(2)/P} = 4.2$ Hz $^2J_{H(2)/P} = 15$ Hz

Chemical equilibration **3** ⇌ **4** was successfully effected with basic catalysis using ethanolic sodium ethoxide (Equation 3). Integration of the signals for H(2) in the proton NMR spectra served for the analysis of the diastereomer ratio and afforded an average value of 0.99 ± 0.03 kcal/mol for the conformational free energy difference [3]; this result is in excellent agreement with that obtained

by the weighted-average coupling constant method.

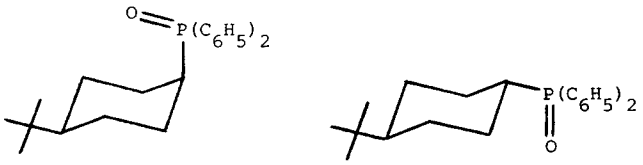
ESTIMATION OF THE MAGNITUDE OF THE ANOMERIC EFFECT IN 1

Because the magnitude of the anomeric effect is frequently defined as the difference between the free energy difference for the equilibrium studied and the conformational energy value for the same substituent in cyclohexane [5], a study was undertaken to estimate the conformational preference of the diphenylphosphinoyl group in cyclohexane [9] (Equation 4).



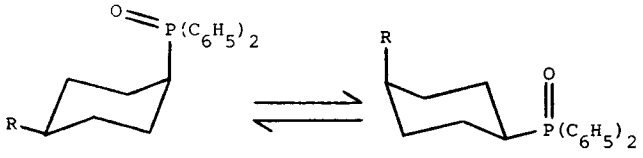
5-axial 5-equatorial (4)

Carbon-13 NMR spectroscopic comparison of **5** with anancomeric **6** and **7** by means of Eliel's equation [$K = (\delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax})$] indicated the equilibrium **5**-axial $\rightleftharpoons$ **5**-equatorial to be highly biased, with a predominance of the equatorial conformer too large to quantify.



6 **7**

Equilibrium constants closer to unity were observed for **8** and **9** which incorporate counterpoise substituents, thus permitting a more precise calculation of $\Delta G°$ (Equation 5).



Axial Equatorial (5)

8, R = CH_3
9, R = C_6H_5

With **8**, the ^{13}C chemical shifts for the methyl group and C(1) were convenient for use in Eliel's equation, giving an average $-\Delta G°[P(O)(C_6H_5)_2]$ = 2.74 ± 0.08 kcal/mol at ambient temperature in solvent chloroform; this $-\Delta G°$ value refers to the process in Equation 4 [9].

Direct observation of the two conformers **9**-axial and **9**-equatorial was possible at low temperature, and the equilibrium constant was then readily obtained by measurement of signal intensities. In this way, the equilibrium constant for **9** was found to be 2.9, favoring equatorial phenyl; this implies $-\Delta G°[P(O)(C_6H_5)_2]$ = 2.46 kcal/mol at −80°C in deuterated dichloromethane. The smaller value at low temperature is probably due to an entropy effect: an axial diphenylphosphinoyl group is conformationally constrained to rotamers with the P-O bond above the cyclohexane ring, whereas an equatorial diphenylphosphinoyl substituent is apparently free to rotate fully around the C-P bond; therefore, the $T\Delta S°$ term increasingly favors the equatorial conformer as the temperature becomes higher. From the conformational free energy differences at room temperature (27°C) and at −80°C, a $\Delta S°$ = +2.6 cal/deg · mol and $-\Delta H°$ = 1.96 kcal/mol are obtained [9].

When the magnitude of the S-C-P(O) anomeric effect is expressed as the difference of $\Delta G°$ in cyclohexane (−2.74 kcal/mol) and the system studied (**1**; + 1.0 kcal/mol), a value equal to 3.74 kcal/mol is estimated. There is, of course, a well-recognized difficulty with evaluation of the anomeric effect in this fashion [10]. In the system at hand, the steric requirement of a group at the two position of the 1,3-dithiane is generally smaller (because of the long C-S bonds) than the steric requirement in a cyclohexane.

Theoretical estimation of the purely steric interactions in the axial conformation of **1** was accomplished in two ways:

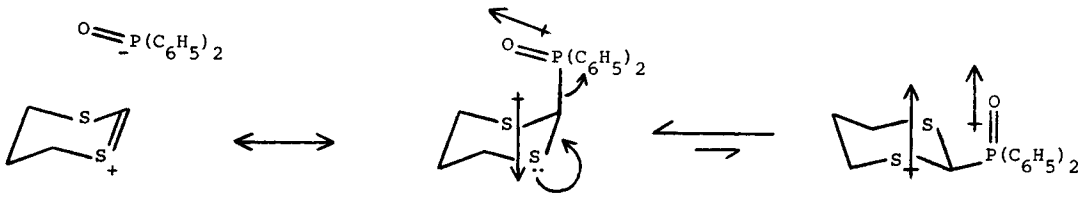
1. Application of the Hill equation [11] to the precise structural data of **1**-axial provided $\Delta H°$ = 1.25 kcal/mol, to which was added the entropy term, $T\Delta S°$ = (298°K) (2.6 cal/deg · °K) = 0.78 kcal/mol; therefore, the reference $\Delta G°$ (steric $\Delta G°$) from which to estimate the magnitude of the anomeric effect (Equation 6) was estimated as −2.03 kcal/mol. Then, since

$$\text{anomeric effect} = -\Delta G°_{\text{steric}} + \Delta G°_{\text{observed}} \quad (6)$$

the magnitude of the anomeric effect would amount to 3.03 kcal/mol [9].

2. It has been shown [12] that the $\Delta G°$ (2-*tert*-butyl) in 1,3-dithianes is about 60% of $\Delta G°$ (*tert*-butyl) in cyclohexane. Thus, applying Franck's methodology [13], the expected size of the diphenylphosphinoyl group in **1** is 60% of 2.74 kcal/mol [9], which affords an anomeric effect equal to 1.0 + (0.60 × 2.74) = 2.64 kcal/mol [14, 15].

In conclusion, estimates (1) and (2), although admittedly crude, afford quite similar values for the magnitude of the anomeric effect present in **1**: close to 3 kcal/mol, which is one of the largest yet recorded [16].



SCHEME 2

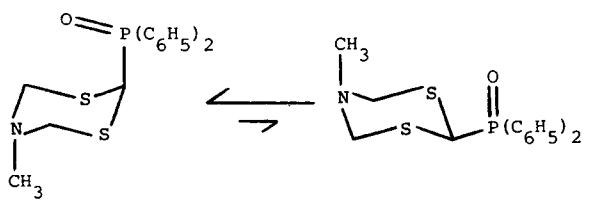
INTERPRETATION OF THE S-C-P(O) ANOMERIC EFFECT OPERATIVE IN 2-(DIPHENYLPHOSPHINOYL)-1,3-DITHIANE

Five distinct mechanisms have been examined to explain the strong anomeric effect present in **1**. All these hypotheses have some experimental or theoretical backing, but all are also suspect because of evidence contrary to expectation. (Of course, no argument can be advanced in favor or against the theory no one has thought of yet!)

1. Most commonly, the anomeric effect has been rationalized in terms of stabilization by *dipole-dipole interaction* [17]. According to this interpretation, electrostatic dipole/dipole repulsion disfavors the equatorial conformer while the dipole/dipole attraction should favor the axial conformer in the equilibrium such as that depicted in Scheme 2. Thus, if dipole/dipole interactions were dominant in the conformational equilibria of **1** (and **3** $\rightleftharpoons$ **4**), it would be expected that the contribution of the equatorial form should increase with increasing dielectric constant of the medium [10]. In fact, the results did not show the expected solvent effect (Table 1 [3]); rather, they gave an erratic trend, which hints at the simultaneous participation of several effects.

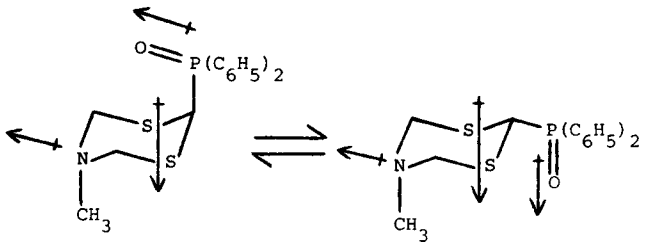
In contrast with our results, Mikolajczyk's group [7] reported a good inverse correlation between the dielectric constant of the solvent and $\Delta\delta_{ax/eq}$ for the C(4, 6) methylene protons: $\Delta\delta$ increased in less polar solvents. Assuming a direct relationship between $\Delta\delta(H_{4,6ax/eq}]$ and the amount of axial **1** [2, 3], this could be evidence supporting the dipole/dipole interaction.

In this respect, it is interesting that the 1.0 kcal/mol preference for axial **1** decreases to 0.53 kcal/mol in the analogous dithiazine **11** [18] (Equation 7).



(7)

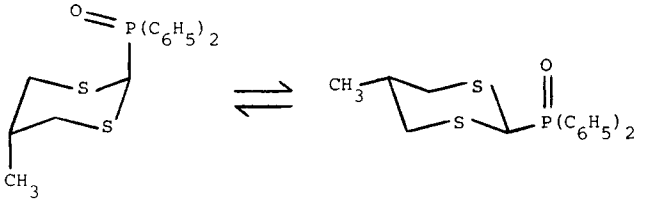
The smaller anomeric effect in the dithiazine vis-à-vis the dithiane is not due to increased steric repulsion between the axial substituent at C(2) and the methylene groups at C(4, 6) [19]. Because the axial disposition of the *N*-alkyl group in the dithiazine [20] causes some cancellation of the ring dipole encountered in the 1,3-dithiane ring ($\mu_{dithiazine}$ = 1.47 D vs. $\mu_{dithiane}$ = 2.09 D), it can be argued that the smaller anomeric effect observed in **11** is the consequence of a less important dipole/dipole component stabilizing the axial conformer (Equation 8). In addition, the P=O and N dipoles are nearly parallel and therefore repulsive for axial P, as shown in Equation 8.



(8)

2. It is remarkable that the axial preference of the diphenylphosphinoyl group decreases substantially in trifluoroacetic acid (Table 1). This very

TABLE 1 Solvent Effect on the Conformational Energies ($\Delta G°$) in *trans*-2-(Diphenylphosphinoyl)-5-methyl-1,3-dithiane (**10**)[a]

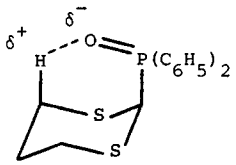


Solvent	ε	$\Delta G°_{eq \rightleftharpoons ax}$,[b] (kcal/mol)
$CDCl_3$	4.7	1.07
CF_3CO_2D	8.2	0.30
CD_2Cl_2	8.9	1.12
CD_3COCD_3	20.7	1.74
CD_3CN	37.5	1.06
CD_3SOCD_3	48.9	1.78

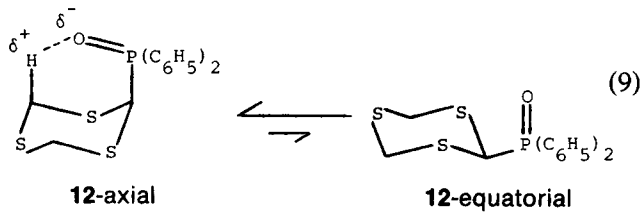
[a] The methyl group in **10** serves as a counterpoise, so that the equilibrium constant is close to unity, permitting a more precise calculation of $\Delta G°$ than would be possible in **1**.

[b] These values were estimated by taking into account the conformational preference of the 5-methyl group: 1.07 kcal/mol [12].

acidic solvent is likely to transfer a proton to the phosphoryl oxygen, and the stability present in **1**-ax is thereby evidently lost. It seems possible that protonation abolishes some *electrostatic attractive interaction between the phosphoryl oxygen and the axial hydrogens* in **1**-ax [2]. This argument has been advanced based on the nonbonded distances between the phosphoryl oxygen and the axial hydrogens H(4,6$_{ax}$) in axial 1,3,5-trithiane **2**-ax [7], and from the estimation of the attractive Coulombic interaction in **1**-ax [21].



Experimental support for this hypothesis comes from the conformational behavior of 2-(diphenylphosphinoyl)-1,3,5-trithiane (**12**), which shows an even higher predominance of the axial conformer [3]. This result is particularly interesting in view of the fact that the anomeric effect observed in trithianes is generally smaller than that in dithianes [16, 22]. The result can be rationalized in terms of a stronger electrostatic interaction in **12**-ax with its more acidic H(4,6) (Equation 9).



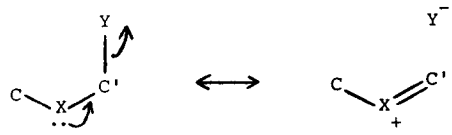
(9)

12-axial **12**-equatorial

Contrary to this argument stands, however, the decreased axial preference in **11** (see above), where the 5-aza group should also lead to increased acidity of H(4,6).

The hypothesis cannot explain either the rather large effects of dimethylsulfoxide (DMSO) and acetone favoring the axial isomer. In fact, these solvents could be expected to compete for the H(4,6) hydrogens, causing a weakened electrostatic attraction in axial P(O)Ph$_2$, contrary to observation (Table 1).

3. More recently, the anomeric effect has been rationalized in terms of *delocalization of the lone pair on the endocyclic heteroatom into the antiperiplanar (axial) adjacent polar bonds* [23]. According to this interpretation, in gauche (axial) C-X-C′-Y systems the C′-X distances are significantly shorter than normal while the C′-Y bond lengths are longer than normal (Equation 10).



(10)

TABLE 2 Selected Interatomic Distances in **1**-Axial and **4** (Equatorial) with Standard Deviations in Parentheses [24]

	1-*Axial*	**4** (Equatorial)
S(1)-C(2)	1.809(3)	1.810(4)
C(2)-P	1.825(3)	1.840(4)
P-O	1.486(2)	1.481(3)

Comparison of the structural data of **1** (axial) [2] and **4** (equatorial) was made in order to examine the possible importance of $n_S \rightarrow \sigma^*_{C\text{-}P}$ interactions which, if significant, would be manifested in shortened C-S and elongated C-P distances in the axial vs. equatorial isomer. Selected bond lengths for **1** and **4** are given in Table 2. The observation [24] that the C-P distance in **4** (equatorial) appears to be significantly longer than that in **1** (axial), as well as the lack of any significant difference in the mean S(1)–C(2) lengths, is *contrary* to expectations if an $n_S \rightarrow \sigma^*_{C\text{-}P}$ interaction makes an important contribution to the preferred axial conformation in **1**.

Additional structural evidence against the importance of $n_S \rightarrow \sigma^*_{C\text{-}P}$ hyperconjugation was observed in **2**-axial [7] and *cis*-2-(diphenylphosphinoyl)-5-*t*-butyl-1,3-dithiane [25]; these compounds exhibited *normal* C-P and C-S bond lengths.

4. A most interesting observation suggests, however, some form of electron transfer to the axial phosphinoyl group. Indeed, the aromatic ring ^{13}C chemical shifts for the ortho and para carbons in the axial isomers **1** and **3** appear at significantly higher fields than those in equatorial **4** [3] (Table 3). By contrast, the signal for the *meta* carbons in **1**, **3**, and **4** are essentially constant. These results are indicative of increased electron density at phosphorus in the axial isomers. Because the crystallographic data are contrary to a $n_S \rightarrow \sigma^*_{C\text{-}P}$ mechanism (see above), an alternative explanation is called for.

In view of the importance of through-space 2p-3d overlap effects between methoxy or dimethylamino groups and phosphorus in various organophosphorus compounds [26], *through-space 3p-3d electron donation from sulfur to phosphorus* might help to account for the preferred axial orientation of the phosphorus moiety in **1** and **3**. Indeed, the P-S distance of ca. 3.0 Å in **1**-ax is much less

TABLE 3 Room Temperature ^{13}C NMR Signals for the Aromatic Carbons in Compounds **1**, **3**, and **4**

Compound	C_{ipso}	C_{ortho}	C_{meta}	C_{para}
1	132.17	131.07	128.30	131.69
3	—[a]	130.94	128.28	131.49
4	—[a]	131.83	128.16	132.25

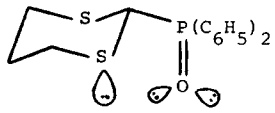
[a] Obscured by baseline noise.

than the sum of the van der Waals radii (3.75 Å) of P and S, and therefore a bonding interaction may be operative.

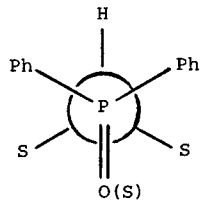
A condition implicit in this proposition is that the orientation of the S_{3p} and P_{3d} orbitals is such that overlap is favorable in **1**-ax but not so in **1**-eq.

The observation that 2-(triphenylphosphonium)-1,3-dithiane exists largely in the equatorial conformation, has been interpreted by Mikolajczyk et al. [27] as inconsistent with the 3p-3d through-space orbital interaction. However, the steric demands of an axial triphenylphosphonium group must be so large that such a model is probably inadequate.

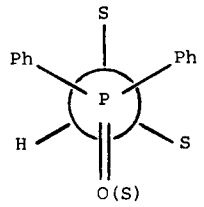
5. Of course, the predominance of **1**-axial over **1**-equatorial may not be due to a stabilizing effect in the axial isomer but rather to a destabilizing interaction in the equatorial isomer. In fact, Mikolajczyk et al. [28] have proposed a *repulsive interaction between the lone pairs on sulfur and on the phosphoryl oxygen in the equatorial conformation.* It should be pointed out that such an effect would be a particular example of the repulsive gauche effect [29, 30].



In this respect, the experimental evidence [29, 30] indicates that such a gauche effect is expected to be repulsive in S/O and particularly S/S segments. It is therefore surprising that equatorial **4** [24] as well as equatorial 2-(diphenylthiophosphinoyl)-1,3,5-trithiane [31] adopt a gauche orientation among heteroatoms (I) rather than one in which the presumed repulsion could be avoided, at least in part (II).



(I)



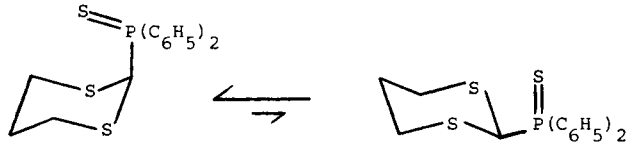
(II)

This finding may be hard to reconcile with the proposed repulsive gauche effect in **1**-equatorial.

EVALUATION OF THE S-C-P(S) ANOMERIC EFFECT

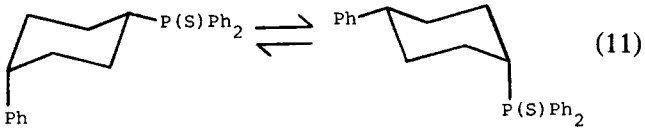
2-(Diphenylthiophosphinoyl)-1,3-dithiane (**13**) was prepared from 1,3-dithiane, *n*-butyllithium and chlorodiphenylphosphine under nitrogen atmosphere; the phosphine intermediate was then treated with 1 equivalent of elemental sulfur. Assignment of the proton NMR spectrum of **13** indicated a large (ca. 0.8 ppm) chemical shift difference between axial and equatorial protons at C(4,6) [32]. This observation is important because finding $\Delta\delta_{ax/eq}$ (H(4,6)) = 1.2 ppm in **1** led to the discovery of the strong S-C-P(O) anomeric effect [2].

To quantify the **13**-ax ⇌ **13**-eq equilibrium, the conformationally fixed derivatives **14** and **15** (Scheme 3) were prepared and equilibrated with ethanolic sodium ethoxide; an average value of 0.05 ± 0.03 kcal/mol for the conformational free energy difference was calculated. This result was then averaged with that obtained by the weighted average coupling constant method ($\Delta G°$ = 0.24 kcal/mol), and therefore a $\Delta G°$ [$(C_6H_5)_2P(S)$] = 0.15 ± 0.1 kcal/mol was obtained at ambient temperature [32]. This value is somewhat smaller than the $\Delta G°_{25°C}$[$(C_6H_5)_2P(S)$] = 0.50 kcal/mol obtained by Mikolajczyk et al. from the equilibration (MeONa/MeOH) of *cis*- and *trans*-2-diphenylthiophosphinoyl)-5-*tert*-butyl-1,3-dithiane [27].



13-axial **13**-equatorial

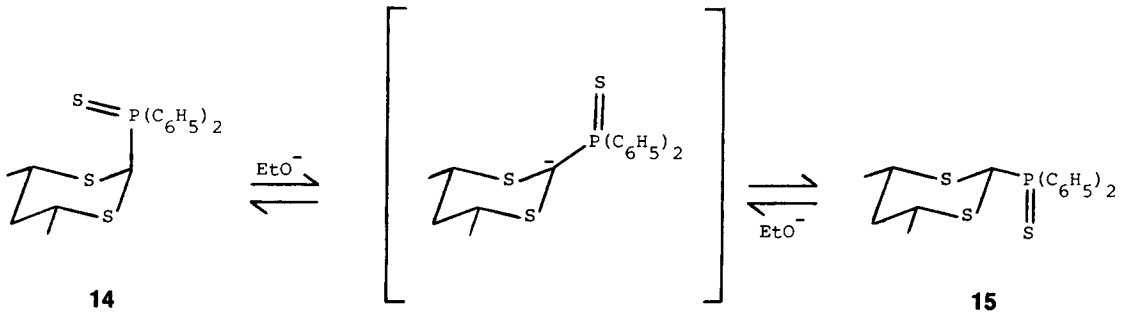
For comparison, the conformational energy of the diphenylthiophosphinoyl group in cyclohexane (its A-value) was determined from NMR spectroscopic comparison of mobile (*cis*-4-phenylcyclohexyl)diphenylphosphine sulfide (**16**) with anancomeric **17** and **18** by means of Eliel's equation [33]; this permitted a calculation of $\Delta G°$ for equation 11: $\Delta G°$(**16**eq → **16**ax) = 0.74 kcal/mol, and therefore $-\Delta G°$ [$Ph_2P(S)$] = 3.61 kcal/mol at 27°C in solvent chloroform [32, 34].



(11)

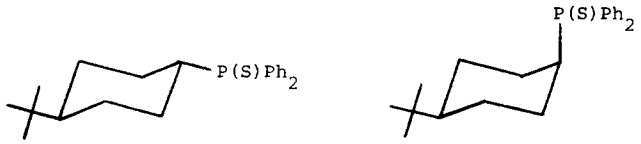
16-equatorial **16**-axial

The conformational energy (A-value) for the diphenylthiophosphinoyl group of 3.61 kcal/mol is remarkably large and falls in the scarcely populated region between phenyl ($-\Delta G°$ = 2.87 kcal/mol [34]) and *tert*-butyl ($-\Delta G°$ = 4.9 kcal/mol [35]). Nevertheless, variable temperature NMR, $Eu(fod)_3$ experiments, and single-crystal x-ray diffraction studies showed that the axial thiophosphinoyl substituent in **18** does not engender a palpable equilibrium between chair and flexible (boat, twist) conformations [32].



14 15

SCHEME 3

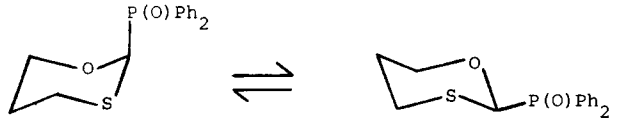


17 18

When the magnitude of the anomeric effect present in dithiane **13** is estimated according to Franck's methodology [13], then 60% of 3.61 kcal/mol (estimated pure steric effect of axial diphenylthiohosphinoyl group) must be added to 0.15 kcal/mol ($\Delta G°$ of **13**-ax $\rightleftharpoons$ **13**-eq equilibrium) to afford a value of 2.32 kcal/mol, for the anomeric effect originated from the S-C-P(S) segments in **13**. This value is somewhat smaller than the one found for S-C-P(O) in **1** (see above).

CONFORMATIONAL PREFERENCE OF THE 2-DIPHENYLPHOSPHINOYL GROUP IN 1,3-OXATHIANE

This section describes the conformational analysis of 2-(diphenylphosphinoyl)-1,3-oxathiane (**19**), which incorporates the O-C-P(O) segment (Equation 12). This study is of interest from several points of view: (*a*) the evaluation of the relative ability of first- and second-row elements on anomeric interactions is just beginning to be explored [36], (*b*) O-C-P segment are ubiquitous in biomolecules, and have been shown to give rise to remarkable stereoelectronic effects [37], and (*c*) the attained information is relevant to the comprehension of the S-C-P anomeric effect [3, 28].



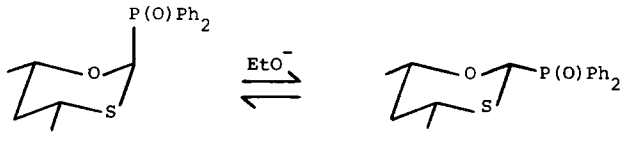
(12)

19-axial 19-equatorial

Both the Mikolajczyk [38] and Juaristi [39] groups have reported spectroscopic and crystallographic evidence for a lack of manifestation of an anomeric effect in **19**; i.e., the equatorial conformer predominates.

Distinct features of the proton NMR spectrum of **19** are a doublet of triplets at 4.27 ppm, and a doublet of doublets at 3.64 ppm; both signals correspond to one proton each. These chemical shifts and coupling patterns indicate that the higher-field signal must be assigned to H(4) in a *predominantly equatorial conformer of* **19**; i.e., the deshielding effect expected from an axial diphenylphosphinoyl group on *syn*-diaxial protons [2, 3] is absent. Also missing is evidence of a γ-gauche upshielding effect at C(4) [38, 39].

A quantitative determination of the conformational energy of the diphenylphosphinoyl group was obtained by Juaristi et al. [40] by chemical equilibration of the anancomeric models **20** and **21** (Equation 13). Ethanolic sodium ethoxide **20** $\rightleftharpoons$ **21** equilibration, and integration of the H(4) and H(6) signals in the proton NMR spectra afforded an **21 : 20** ratio, K = 8.85 ± 1.75, and therefore a $\Delta G°_{55°C}$ [$P(O)Ph_2$] = −1.42 ± 0.12 kcal/mol [40].

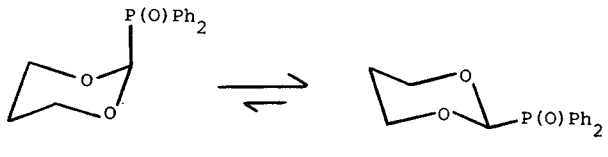


20 21

(13)

CONFORMATIONAL PREFERENCE OF THE 2-DIPHENYLPHOSPHINOYL GROUP IN 1,3-DIOXANE. IS THERE AN O-C-P(O) ANOMERIC EFFECT?

Recently, the lack of manifestation of an anomeric effect in 2-(diphenylphosphinoyl)-1,3-dioxane (**22**) was reported [25, 39–41]; i.e., the equatorial conformer predominates (Equation 14).



22-axial **22**-equatorial (14)

<5% >95% (15)

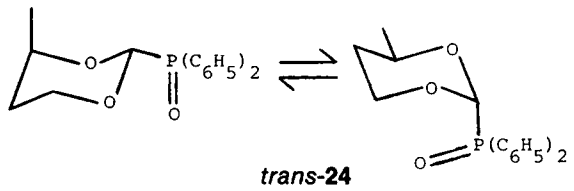
cis-**23**

This result is in contrast again with the strong axial preference of the 2-diphenylphosphinoyl group in 1,3-dithiane, $\Delta G°$ [$P(O)Ph_2$] = +1.0 kcal/mol (Equation 1) [2, 3], and could be surprising because anomeric effects involving second-row elements have been predicted to be much less important than those with first-row elements [36].

Nevertheless, because of the shorter C-O bonds (ca. 1.43 Å) relative to the C-S bonds (ca. 1.82 Å), the steric repulsion of the axial diphenylphosphinoyl group (A-value = 2.74 kcal/mol) could dominate over the O-C-P(O) anomeric effect in **1**. A quantitative evaluation of the conformational preference of the phosphorus substituent was therefore necessary to establish the contribution of an anomeric effect, if any.

cis- and *trans*-2-(Diphenylphosphinoyl)-5-*tert*-butyl-1,3-dioxanes (*cis*- and *trans*-**23**) were prepared as shown in Scheme 4 [42]. ^{13}C and ^{31}P NMR data for *cis*- and *trans*-**23** indicate that the *tert*-butyl group is completely (≳95%) equatorial in *trans*-**23**, but completely axial in the *cis* isomer (Equation 15). Because the conformational energy of the 5-*tert*-Bu in 1,3-dioxane is 1.4 kcal/mol [43], and because $-\Delta G° > 1.7$ kcal/mol in Equation 15, a minimum $\Delta G°$ [$P(O)Ph_2$] ≳3.1 kcal/mol, favoring **22**-eq was determined [42].

More definitive results were achieved in the 4-methyl series, where the methyl group acts as a more demanding counterpoise (2.87 kcal/mol) [43]. The synthesis of *cis*- and *trans*-2-diphenylphosphinoyl-4-methyl-1,3-dioxane (*cis*- and *trans*-**24**) was carried out as shown in Scheme 4. Most useful is the ^{13}C NMR chemical shift for the methyl group (in $CDCl_3$): 21.67 and 18.29 ppm in the *cis* and *trans* isomers, respectively. By comparison, $\delta(CH_3)$ = 16.41 ppm in the pure axial methyl model *trans*-2-*tert*-butyl-4-methyl-1,3-dioxane (*trans*-**25**). Application of Eliel's equation [33] [$K = (\Delta_{eq} - \delta_{mobile})/(\delta_{mobile} - \delta_{ax}) = (21.67 - 18.29)/(18.29 - 16.41) = 1.80$] provided $\Delta G°_{307K}$ = +0.36 kcal/mol (Equation 16), and therefore $\Delta G°_{307K}$ [$P(O)Ph_2$] = −3.23 kcal/mol in the absence of the 4-methyl group (Equation 14) [42].

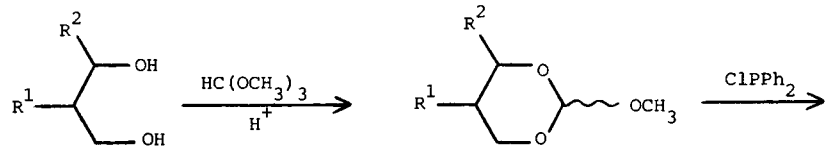


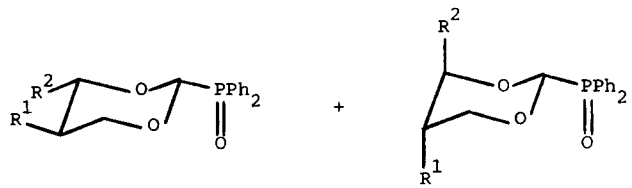
(16)

trans-**24**

Manifestation of an anomeric effect in **1** would require that the magnitude of such an effect over-

SCHEME 4





R^1 = *t*-Bu, R^2 = H: *trans*-**23** + *cis*-**23** (4 : 1)

R^1 = H, R^2 = CH_3: *cis*-**24** + *trans*-**24** (5 : 1)

comes the steric hindrance experienced by axial 2-substituents. For example, the equatorial preference of a methyl group in cyclohexane amounts to 1.74 kcal/mol [44], whereas it increases (by a factor of 2.2) to 3.9 kcal/mol in 2-methyl-1,3-dioxane [43]. Thus, the expected size of the diphenylphosphinoyl group in **1** is ca. 2.2 × 2.74 kcal/mol = 6.0 kcal/mol [13, 15]. The difference between this value and the one experimentally obtained, ca. 3.2 kcal/mol, affords an anomeric effect worth ca. 2.8 kcal/mol! [42].

It is of interest to compare this value with that estimated in **1** (see Estimation of the Anomeric Effect in **1**, above), which affords an anomeric effect equal to 1.0 + (0.60 × 2.74) = 2.64 kcal/mol [15, 42].

By the same token, a 2-methyl group in 1,3-oxathiane shows an equatorial preference of 3.25 kcal/mol [45], larger by a factor of 1.87 than its A-value. The expected equatorial preference of the 2-diphenylphosphinoyl group in 1,3-oxathiane is therefore 1.87 × 2.74 = 5.12 kcal/mol. The experimental value, 1.42 kcal/mol [40], suggests an anomeric effect of ca. 3.7 kcal/mol [15, 42].

Seen in this light, it appears that the anomeric effects operative in O-C-P(O) and S-C-P(O) segments are of similar magnitude, close to 3 kcal/mol [16]; nevertheless, the nature of the O-C-P(O) and S-C-P(O) anomeric interactions could be different.

CLOSING REMARKS

The finding of a very strong S-C-P(O) anomeric effect in 1982 [2] has provided a driving force for renewed efforts directed to the understanding of the anomeric effect, particularly when involving second- and lower-row elements. The fact that no single interpretation of the nature of the X-C-P anomeric interactions seems to fit all experimental facts points to the need of more ingenious models and experiments, as well as additional theoretical studies to evaluate the relative contribution of the factors responsible for the anomeric effect.

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