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Theoretical Examination of the S−C−P Anomeric Effect

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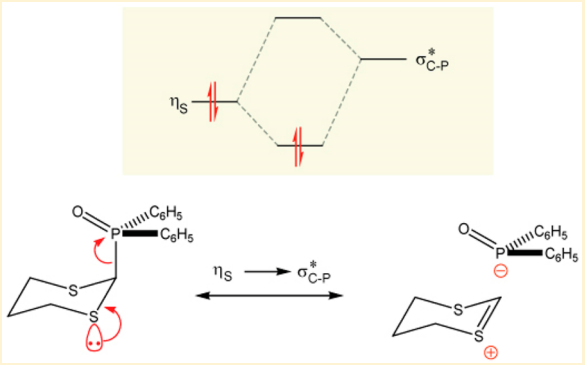
Supporting Information

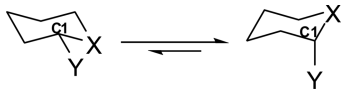
ABSTRACT: Three decades after the discovery of a strong S−C−P anomeric effect in 2-diphenylphosphinoyl-1,3-dithiane (**1**) and 2-trimethylphosphonium-1,3-dithiane (**4**), its definitive interpretation is still lacking. The present study reports DFT geometry optimizations of **1**-ax, **1**-eq, **4**-ax, and **4**-eq, which do reproduce the S−C−P anomeric effect in **1** and **4**, worth 5.45 and 3.08 kcal/mol, respectively (in chloroform solvent). Weinhold's NBO analysis supports the existence of dominant $n_X \rightarrow \sigma^*_{C-Y}$ stereoelectronic interactions that stabilize the axial conformers.



Since its first recognition six decades ago, the "anomeric effect" has become one of the most frequently used concepts advanced to explain the conformational behavior, structural properties, and even the reactivity of saturated heterocyclic systems.[1] Nevertheless, the origin of the anomeric effect is still a matter of debate,[2] and it is evident that further investigation of this important effect is required.

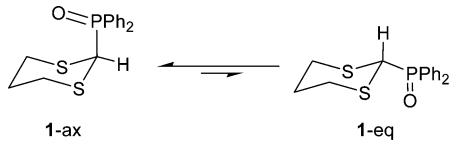
The presence of lone electron pairs in heterocyclic compounds can have pronounced effects on the conformation of substituted saturated heterocycles. In particular, the interaction of electron-withdrawing anomeric substituents [electronegative groups localized at C(1)] with endocyclic lone electron pairs induces a preference by these substituents *to adopt the axial instead of the equatorial orientation*. This conformational effect was initially described by Edward[3] and later by Lemieux and Chü[4] in what became to be known as the *anomeric effect* (Scheme 1).

Scheme 1. Preference of Electronegative Substituents at the Anomeric Position To Adopt the Axial Orientation

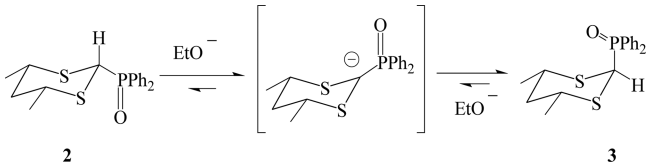


In one explanation of this conformational effect, a stabilizing interaction between a lone electron pair on the ring heteroatom (X) and the antiperiplanar antibonding orbital of the bond connecting the axial substituent (Y) at the anomeric carbon ($n_X \rightarrow \sigma^*_{C-Y}$) has been proposed. This interaction results in lengthening of the C−Y bond as well as shortening of the C−X bond as a consequence of its increased double-bond character.[5] In this regard, some time ago proton NMR spectroscopic data showed significant deshielding of the *syn*-axial protons at C(4) and C(6) in 2-diphenylphosphinoyl-1,3-dithiane (**1**), which suggested an *axial* conformation of the diphenylphosphinoyl group (Scheme 2).[6] In order to quantitate this conformational effect, conformationally fixed **2** (equatorial model) and **3** (axial model) were prepared, and their chemical equilibration under basic catalysis (in ethanol solvent) afforded $\Delta G^\circ = +1.0$ kcal/mol, with axial **3** being more stable than equatorial **2** (Scheme 3).[7] Comparison of the structural data for **1**-ax and the equatorial analogue **2** did not exhibit the expected (in terms of an $n_S \rightarrow \sigma^*_{C-P}$ hyperconjugative interaction)

Scheme 2. Predominance of the Axial Conformation in the Conformational Equilibrium of 1



Scheme 3. Chemical Equilibrium of Conformationally Fixed Models 2 and 3



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contraction of the S−C(2) bond and lengthening of the C(2)−P bond in **1**-ax.[8]

Among various subsequent studies aiming to explain the nature of the "anomeric effect in the S−C−P molecular segment",[9,10] in 1986 it was found that the axial preference of the diphenylphosphinoyl group in **1** (Scheme 1) vanishes in trifluoroacetic acid as the solvent. This finding could be in line with neutralization of the electrostatic attractive interaction between the phosphoryl oxygen and the axial hydrogens H(4) and H(6ax) in **1**-ax upon protonation of the phosphoryl oxygen. (In principle, protonation should also increase the effective size of the phosphoryl group; however, attachment of the proton to the phosphoryl group away from the heterocyclic ring should lead to a minimal increase in steric repulsion).[7]

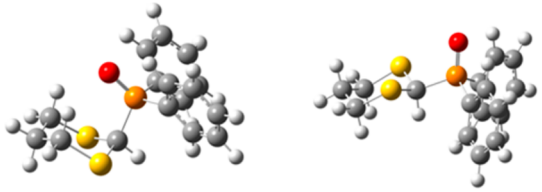
Indeed, Cuevas[11] found computational evidence for an electrostatic attractive interaction between the phosphoryl oxygen and the 1,3-*syn*-diaxial hydrogen atoms in axial 2-dimethylphosphinoyl-1,3-dithiane. However, the strong anomeric effect observed in the trimethylphosphonium analogue **4**,[12] where the phosphorus substituent is unable to participate in a hydrogen-bonding interaction with the *syn*-diaxial hydrogens at H(4) and H(6) (Scheme 4) suggests the participation of an additional effect.

Scheme 4. The Free Energy Difference, ΔG° = +0.36 kcal/mol, Is Indicative of a Substantial S−C−$^+$PMe$_3$Cl$^-$ Anomeric Effect Worth at Least 2.2 kcal/mol[12]

4-ax **4**-eq

With the arrival of powerful computational techniques,[1q] the aim of the present work was to answer three questions: (1) Can theoretical calculations reproduce the experimental anomeric effect manifested experimentally in the conformational behavior of 2-diphenylphosphinoyl-1,3-dithiane (**1**-ax ⇄ **1**-eq; Scheme 2) and its trimethylphosphonium analogue **4** (Scheme 4)? (2) Can natural bond orbital (NBO) calculations provide evidence for stereoelectronic interactions as the origin of those conformational equilibria? (3) Can comparison with calculated conformational equilibria of cyclohexyl analogues provide information on the magnitude of the S−C−P anomeric effect in these systems?

The optimized geometries of axial and equatorial **1** at the B3LYP/6-311+G(d,p) level of theory are presented in Figure 1 and Table 1. The C(2)−P(O) bond in the axial isomer **1**-ax (1.867 Å) and the C(2)−P(O) bond in equatorial **2** (1.867 Å)



1-ax **1**-eq

Figure 1. B3LYP/6-311+G(d,p)-optimized structures of 2-diphenylphosphinoyl-1,3-dithiane in the axial (**1**-ax) and equatorial (**1**-eq) conformations.

Table 1. B3LYP/6-311+G(d,p)-Optimized Geometrical Parameters of 2-Diphenylphosphinoyl-1,3-dithiane in the Axial (1-ax) and Equatorial (1-eq) Conformations (Bond Distances in Å and Bond Angles in deg)

bond/angle	**1**-ax	**1**-eq
C(2)−P	1.867	1.867
C(2)−S	1.835−1.836	1.837−1.838
P═O	1.505	1.497
C(4)−S	1.841−1.842	1.837−1.838
C(4)−C$_5$	1.528−1.529	1.529
S−C(2)−S	114.7	114.0
C(2)−P−O	113.0	114.8
C(2)−S−C(4)	100.8−100.9	98.0
S−C(4)−C(5)	114.1−114.2	114.4−114.5
C(4)−C(5)−C(6)	113.4	113.8

are calculated to be exactly the same. Also, the ring C(2)−S bonds in **1**-ax and **2** (equatorial) are essentially identical (1.836 ± 0.002 Å in both isomers). Experimentally, the X-ray crystallographic data recorded in 1984 afforded 1.825 Å for axial C(2)−P and 1.840 Å for equatorial C(2)−P. On the other hand, the C(2)−S bond lengths are 1.809 Å in **1**-ax and 1.809 Å on average in equatorial model **2**.[8] As indicated above, both the experimental and calculated structural data are not in line with the anticipated consequences of an $n_S \rightarrow \sigma^*_{C-P}$ stereoelectronic interaction; that is, substantial shortening of the S−C(2) bond and lengthening of the C(2)−P(O) bond in **1**-ax relative to **1**-eq was expected.

The natural charges obtained from the NBO calculations are H(4)/(6) = +0.235/0.236 and O = −1.100, and the O···H distances are 2.503/2.552 Å, in line with the existence of H-bonding [i.e., substantial negative charge present on the phosphoryl oxygen and O···H distances shorter than the sum of van der Waals radii (1.2 + 1.6 = 2.8 Å)].

Most relevant, the DFT calculations do reproduce the S−C−P anomeric effect in diphenylphosphinoyl-1,3-dithiane **1** and trimethylphosphonium-1,3-dithiane **4**, that is, the *tendency* of the phosphorus substituent to adopt the axial orientation. Indeed, according to calculations at the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) levels of theory, in solvent ethanol at 294 K the conformer with the diphenylphosphinoyl group in the axial position (**1**-ax in Scheme 2) is lower in free energy, with ΔG° = +1.36 kcal/mol and +1.30 kcal/mol, respectively. These values are very close to the experimentally observed value of ΔG°_{294K} = +0.99 kcal/mol in ethanol.[6,7] Nevertheless, at the B3LYP/6-311+G(d,p) level, the calculated ΔG°_{298K} value of +2.90 kcal/mol in chloroform is significantly larger than the experimentally obtained value. The calculated conformational free energy difference in the gas phase is even larger (+3.8 kcal/mol), probably as the result of overestimated hydrogen-bonding interactions between the phosphoryl oxygen and the axial hydrogens on C(4) and C(6) that stabilize the axial isomer.

The optimized geometries of axial and equatorial 2-trimethylphosphonium-1,3-dithiane chlorides (**4**-ax and **4**-eq), at the B3LYP/6-311+G(d,p) level of theory, are presented in Figure 2 and Table 2. Most relevant is the observation that the C(2)−P$^+$Me$_3$Cl$^-$ bond lengths in the axial isomer **4**-ax and equatorial isomer **4**-eq are the same within the limits of anticipated margin of error (1.866 vs 1.859 Å, respectively). Similarly, the ring C(2)−S bonds in **4**-ax and **4**-eq are also calculated to be identical (1.84 Å in both isomers).

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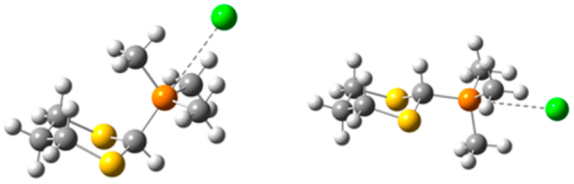

4-ax **4**-eq

Figure 2. B3LYP/6-311+G(d,p)-optimized structures of 2-trimethylphosphonium-1,3-dithiane chlorides in the axial (**4**-ax) and equatorial (**4**-eq) conformations.

Table 2. B3LYP/6-311+G(d,p)-Optimized Geometrical Parameters of 2-Trimethylphosphonium-1,3-dithiane Chloride in the Axial (4-ax) and Equatorial (4-eq) Conformations (Bond Distances in Å and Bond Angles in deg)

bond/angle	4-ax	4-eq
C(2)−P	1.866	1.859
C(2)−S	1.837	1.840
P−C(2)	1.806	1.806
C(4)−S	1.839	1.838
C(4)−C(5)	1.527	1.528
S−C(2)−S	116.0	114.2
C(2)−P−C	112.1	109.0
C(2)−S−C(4)	103.1	98.7
S−C(4)−C(5)	114.5	114.4
C(4)−C(5)−C(6)	113.3	113.8

At the B3LYP/6-311+G(d,p) level of theory, in chloroform solvent the conformer with the trimethylphosphonium group in the axial position (**4**-ax in Scheme 4) is calculated to be 0.96 kcal/mol higher in energy, i.e., $\Delta G^{\circ}_{298K} = -0.96$ kcal/mol. This estimate is significantly different than the experimentally obtained value in chloroform, $\Delta G^{\circ}_{298K} = +0.36$ kcal/mol,[12] but still supportive of the existence of a substantial S−C−P anomeric effect in **4** (see below).

In contrast to the observations made with the diphenylphosphinoyl analogue (see above), where the preference for the axial isomer is significantly larger in the gas phase relative to the solution data, the calculated conformational free energy difference for the trimethylphosphonium chloride derivative in the gas phase is quite similar to the value obtained in chloroform ($\Delta G^{\circ}_{298K} = -0.70$ vs -0.96 kcal/mol, respectively), which is in line with anticipation when one takes into account the nonexistence of hydrogen-bonding interactions between the phosphorus substituent and the axial hydrogens on C(4) and C(6) in the trimethylphosphonium system.

As has been shown by Alabugin,[13e,i] the NBO method developed by Weinhold and co-workers[14] is very useful for the study of hyperconjugation. In particular, NBO analysis gives an estimate of the magnitude of the delocalizing interactions that weaken the axial C−P bonds. The energies of interest (E_{del}) are obtained by deletion of the corresponding Fock elements followed by recalculation of the wave function. Table 3 lists values of E_{del} for the main hyperconjugative interactions in dithianes **1**-ax, **1**-eq, **4**-ax, and **4**-eq along with the energy differences between the donor and acceptor orbitals of interest ($\Delta E_{d/a}$). As expected, an inverse relationship between the energy gap and the magnitude of the two-electron/two-orbital hyperconjugative interaction is observed.

Table 3. Selected Hyperconjugative Interactions (E_{del}) in 2-Diphenylphosphinoyl-1,3-dithiane (1-ax and 1-eq) and 2-Trimethylphosphonium-1,3-dithiane (4-ax and 4-eq)

	donor orbital	acceptor orbital	E_{del} (kcal/mol)	$\Delta E_{d/a}$ (hartrees)
1-ax	$n_{S(ax)}$	$\sigma^*_{C-P(ax)}$	3.86	0.41
	$n_{S(eq)}$	$\sigma^*_{C-P(ax)}$	1.65	0.81
	$n_{S(ax)}$	$\sigma^*_{C(2)-S}$	5.31	0.37
	$n_{S(eq)}$	$\sigma^*_{C(2)-S}$	1.97	0.77
	$\sigma_{C(4,6)-S}$	σ^*_{C-P}	−	−
1-eq	n_S	$\sigma^*_{C-P(eq)}$	−	−
	$n_{S(ax)}$	$\sigma^*_{C(2)-S}$	6.88	0.37
	$n_{S(eq)}$	$\sigma^*_{C(2)-S}$	1.29	0.77
	$\sigma_{C(4,6)-S}$	$\sigma^*_{C-P(eq)}$	1.87	0.76
4-ax	$n_{S(ax)}$	$\sigma^*_{C-P(ax)}$	4.32	0.40
	$n_{S(eq)}$	$\sigma^*_{C-P(ax)}$	1.58	0.80
	$n_{S(ax)}$	$\sigma^*_{C(2)-S}$	4.25	0.37
	$n_{S(eq)}$	$\sigma^*_{C(2)-S}$	2.50	0.77
	$\sigma_{C(4,6)-S}$	$\sigma^*_{C-P(ax)}$	−	−
4-eq	n_S	$\sigma^*_{C-P(eq)}$	−	−
	$n_{S(ax)}$	$\sigma^*_{C(2)-S}$	6.84	0.37
	$n_{S(eq)}$	$\sigma^*_{C(2)-S}$	1.35	0.77
	$\sigma_{C(4,6)-S}$	$\sigma^*_{C-P(eq)}$	1.85	0.76

Salient observations are the following: (1) $n_S \rightarrow \sigma^*_{C-P}$ stereoelectronic interactions are observed in **1**-ax and **4**-ax but not in **1**-eq or **4**-eq. This observation is in line with anticipation in terms of an efficient stereoelectronic interaction in the axial conformation, where the donor and acceptor interacting orbitals are antiperiplanar to each other. As discussed above, this stereoelectronic interaction is responsible for the S−C−P anomeric effect, which is manifested as the axial predominance of the phosphorus substituents at C(2) in the 1,3-dithiane ring. In this regard, $n_S \rightarrow \sigma^*_{C-H}$ stereoelectronic interactions are rather weak (see Table S-1 in Supporting Information) and can been disregarded in this discussion. (2) By contrast, $n_S \rightarrow \sigma^*_{C(2)-S}$ stereoelectronic interactions are present in both the axial and equatorial isomers, so the stabilizing interaction is equally effective in both orientations of the phosphorus group and has no consequence on the conformational free energy difference of the 2-P-substituted 1,3-dithianes **1** and **4**. (3) On the other hand, antiperiplanar $\sigma_{C(4,6)-S} \rightarrow \sigma^*_{C-P}$ stereoelectronic interactions are effective in equatorial **1**-eq and **4**-eq. This stereoelectronic interaction should weaken the equatorial C(2)−P bonds, which are rendered longer. This may help explain the "anomalous" structural observation that the C(2)−P bond distances are the same in the axial and equatorial isomers of **1** and **4**; that is, $n_S \rightarrow \sigma^*_{C-P}$ stereoelectronic interactions are responsible for the longer C(2)−P axial bonds, but $\sigma_{C(4,6)-S} \rightarrow \sigma^*_{C-P}$ interactions give rise to longer C(2)−P equatorial bonds.

The interpretations advanced above are supported by deletion of the key NBO interactions followed by reoptimization of the geometries with these interactions switched off (NBODEL). In order to reduce computation time, axial and equatorial 2-dimethylphosphinoyl-1,3-dithiane (**5**-ax and **5**-eq, respectively) were used as models for the larger **1**-ax and **1**-eq heterocycles. NBODEL calculations were also carried out on **4**-ax and **4**-eq. The results are summarized in Tables S-3 and S-4 in the Supporting Information. In all cases, application of NBODEL with the key hyperconjugative interactions switched off led to lengthening of the C(2)−S bonds and simultaneous shortening of the C(2)−P bonds, as anticipated in terms of $n_S \rightarrow \sigma^*_{C-P(ax)}$, $\sigma_{C(4,6)-S} \rightarrow \sigma^*_{C-P(eq)}$, and $n_S \rightarrow \sigma^*_{C(2)-S}$ stereoelectronic interactions.

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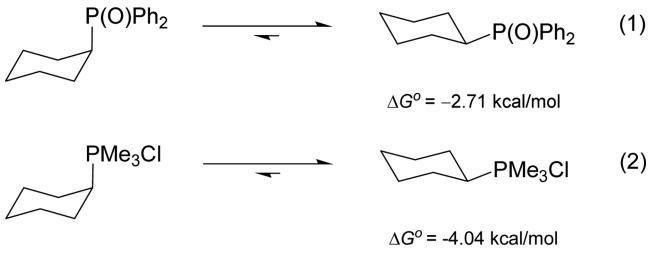
Equations 1 and 2 present the calculated conformational free energy differences for the diphenylphosphinoyl and trimethylphosphonium groups in cyclohexane. The magnitude of the anomeric effect can be estimated by comparison of the



conformational preference of the substituent in the heterocyclic system relative to the conformational preference of the same substituent in cyclohexane (its *A* value).[1] Thus, consideration that the diphenylphosphinoyl group's *A* value is worth 2.74 kcal/mol[15] suggests an anomeric effect worth 2.71 − (−2.74) = 5.45 kcal/mol in **1** (in chloroform). By the same token, since the calculated conformational preference of the trimethylphosphonium group in 1,3-dithiane is −0.96 kcal/mol and the calculated *A* value of the same group is −4.04 kcal/mol (this work), this affords a value of 3.08 kcal/mol for the magnitude of the S−C−P anomeric effect in **4** (in chloroform).

In conclusion, DFT calculations do reproduce the S−C−P anomeric effect in diphenylphosphinoyl-1,3-dithiane (**1**) and trimethylphosphonium-1,3-dithiane (**4**); that is, the *tendency* of the phosphorus substituent to adopt the axial orientation. The natural bond orbital (NBO) method developed by Weinhold and co-workers[14] is a very useful theoretical method for the study of hyperconjugative interactions present in **1** and **4**. In particular, NBO analysis provided the energies of the delocalizing interactions that weaken the axial C−P bonds of interest. In particular, $n_S \rightarrow \sigma^*_{C-P}$ stereoelectronic interactions are observed in **1**-ax and **4**-ax but not in **1**-eq or **4**-eq, as anticipated in terms of an efficient hyperconjugative interaction in the conformation where the donor and acceptor interacting orbitals are antiperiplanar to each other. This stereoelectronic interaction is responsible for the S−C−P anomeric effect, which is manifested as the axial predominance of the diphenylphosphinoyl substituent in **1** as well as the small equatorial preference of the trimethylphosphonium group in **4**. On the other hand, antiperiplanar $\sigma_{C(4,6)-S} \rightarrow \sigma^*_{C-P}$ stereoelectronic interactions are only effective in equatorial **1**-eq and **4**-eq, which may help explain the "anomalous" structural observation that the C(2)−P bond distances are of the same length in the axial and equatorial isomers of **1** and **4**.

Comparison of the calculated conformational preference of the substituent in the heterocyclic system relative to the conformational preference of the same substituent in cyclohexane suggests an anomeric effect worth 2.71 − (−2.74) = 5.45 kcal/mol for the anomeric effect operative in **1**. By the same token, the calculated conformational preference of the trimethylphosphonium group in 1,3-dithiane, −0.96 kcal/mol, and the calculated *A* value of the same group, −4.04 kcal/mol, afford a value of 3.08 kcal/mol for the magnitude of the S−C−P anomeric effect in **4**.

COMPUTATIONAL METHODS

All of the calculations were carried out with the Gaussian 09 suite of programs.[16] All of the energy minima and transition states were fully optimized at the B3LYP/6-311+G(d,p) level of theory.[17−24] Electronic structures were examined using NBO analysis,[13] and hyperconjugative interactions were evaluated by means of the NBO program (version 3.1).[25] Inclusion of solvent was accomplished according to the polarizable continuum model developed by Tomasi and co-workers.[26]

ASSOCIATED CONTENT

Supporting Information

NBO hyperconjugative interactions in **1**-ax, **1**-eq, **4**-ax, and **4**-eq (Table S-1); B3LYP/6-311+G(d,p)-optimized geometries of the compounds studied in this work (Table S-2); and comparison of structural parameters in the optimized geometries, at the HF/6-31G(d) computational level, of **4**-ax, **4**-eq, **5**-ax, and **5**-eq with those optimized geometries obtained by NBODEL with key NBO interactions switched off (Tables S-3 and S-4). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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