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Conformational Analysis of 2-Phosphoryl and 2-Thiophosphoryl 1,3-Heteroanes by Molecular Mechanics Calculations. A Question of the Origin of the Anomeric Effect

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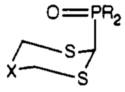
The conformational behavior of 2-phosphoryl-1,3-dioxane, 2-phosphoryl-1,3-dithiane, and 2-thiophosphoryl-1,3-dithiane has been investigated by means of molecular mechanics. The calculations showed that the energy difference, $\Delta E = E^{ax} - E^{eq}$, for the first compound is equal to 7 kJ/mol in favor of the equatorial chair conformation. The axial chair conformer is destabilized by 1,3-syn-axial interactions between the 4,6-methylene groups and the bulky phosphoryl group. By contrast, the equatorial chair conformation of 2-phosphoryl-1,3-dithiane was calculated to be less stable than the axial one by 5.5–8.0 kJ/mol due to repulsive interactions between the lone electron pairs on sulfur and phosphoryl oxygen. The 1,3-syn-axial interactions in the 1,3-dithiane ring play no important role owing to the extended C–S bond lengths. In 2-thiophosphoryl-1,3-dithiane the increased 1,3-syn-axial interactions in the axial conformation and decreased lone electron pair interactions in the equatorial conformation lead to the approximately equal energies of the two conformations and their nearly equal populations.

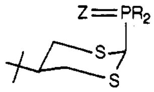
Introduction

A knowledge of the conformational properties of 1,3-heteroanes and determination of the conformational preferences of substituents at the carbon atom 2 in such ring systems are still timely and of interest, especially from the point of view of understanding the origin of the anomeric effect.[1] As pointed out by Eliel and Hutchins[2] in their early paper on the conformation of 2-alkyl-substituted 1,3-dithianes, there are important differences in conformational behavior of cyclohexanes and heteroanes due to the variation in bond lengths, bond angles, and torsional barriers as well as the presence of the lone electron pairs on heteroatoms that replace the methylene groups in the cyclohexane ring. Recently, Juaristi et al.[3] as well as our group[4] have found that the 2-diphenylphosphinoyl and 2-dimethoxyphosphoryl group in 1,3-di- and 1,3,5-trithiane rings (1) show a strong preference for the axial position. Thus, 2-phosphoryl-substituted polythianes represent a new example[5] of the structure in which the anomeric effect is observed.[6]

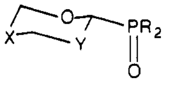


1

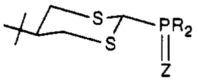
X = CH$_2$, R = Ph
X = S, R = MeO
X = CH$_2$, R = MeO



cis-**2**



3a: X = CMe$_2$, Y = O, R = Ph
3b: X = CMe$_2$, Y = S, R = Ph



trans-**2**

Z = O, S, Se
R = Ph, MeO

However, this finding was 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 *tert*-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 there is no lone electron pair, and the difference in electronegativity between P and C is rather small.

Our subsequent NMR studies of the diastereomeric 2-substituted 5-*tert*-butyl-1,3-dithianes 2[7,8] showed that the tendency to occupy an axial position in a chair conformation is strongest for the P(O) group ($-\Delta G^0 = 3.93$ kJ/mol) and decreases on going to the P(S) ($-\Delta G^0 = 2.09$ kJ/mol) and then to the P(Se) group ($-\Delta G^0 = 1.47$ kJ/mol). Therefore, the conformationally labile 2-thiophosphoryl and 2-selenophosphoryl polythianes exist in a solution as a mixture of axial and equatorial chair conformers as evidenced by the low-temperature ^{31}P NMR spectra.

The accumulated X-ray data[3a,7,8] on 2-phosphoryl-substituted 1,3-di- and 1,3,5-trithianes revealed that the anomeric effect operating in this case is most probably not due to the interaction of the endocyclic sulfur lone electron pairs with the axial P–C(2)σ^* orbital ($n_S \rightarrow \sigma^*_{C-P}$ overlap)

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(6) In accord with the definition: the general preference for the gauche conformation about a carbon–heteroatom bond in systems R–X–C–Y has been termed the generalized anomeric effect; ref 1, p 21.

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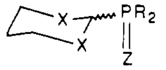
because the expected changes in bond lengths, i.e., the shortening of the C–S bonds and lengthening of the C–P bond, characteristic for this effect, are not observed.

Finally, it is of interest to point out that, in contrast to the 1,3-di- and 1,3,5-trithiane systems, the phosphoryl group in 1,3-dioxane **3a** and 1,3-oxathiane **3b** prefers to be equatorial both in a solution and in the solid state.[9]

This rather complex situation and lack of a reasonable explanation for a strong axial preference of the phosphoryl group in 1,3-dithiane and 1,3,5-trithiane rings prompted us to study the conformational behavior of 2-phosphoryl-1,3-dioxane **4**, 2-phosphoryl-1,3-dithiane **5**, and 2-thiophosphoryl-1,3-dithiane **6** by means of molecular mechanics[10] in the hope that the results of calculations will reveal the main factors that are responsible for the conformational preferences in 1,3-heteroanes discussed above.



4: X = O, Z = O
5: X = S, Z = O
6: X = S, Z = S

Results and Discussion

Potential Function and Parametrization. The potential function of the molecules of **4**, **5**, and **6** includes the energy of nonbonded interactions (E_{nb}), the torsional energy for rotation around single bonds (E_t), the energy of angle deformations (E_{ad}), and the energy of the lone electron pair interactions (E_{lep}). The first energy term in

$$E = E_{nb} + E_t + E_{ad} + E_{lep}$$

this equation was evaluated by means of Dashevskii's potentials.[11] The interaction potential for the phosphorus atom was selected by us earlier[12] and that for the sulfur atom was taken from the work of Nauchitel and Mirskaja.[13]

Rotations around single bonds were assumed to be in the form of 3-fold barrier with the torsional potential constants for the C–C, C–O, C–S, and C–P bond equal to 12, 4, 4, and 14 kJ/mol,[12,13] respectively.

In calculations of the bond angle deformations, we preceded from the assumption that bond angles at C and O are tetrahedral with the constants 122 and 270 kJ/mol·r^2, respectively. An ideal value of the bond angle for the S atom was assumed to be 100°. The parametrization of angle deformations for the P atom, which was also elaborated by us earlier,[14] takes into account nonidentical ideal bond angles (and constants) for the O=PC and C–P–C fragments.

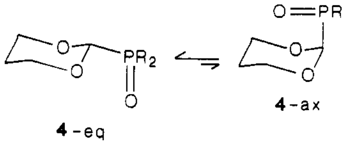
In addition to the three classical energy components discussed above, the potential function of the molecules **4**–**6** contained also the E_{lep} term, which takes into account the interactions of the lone electron pairs as pseudoatoms. The latter were calculated as point charges located at the proper distance from the nuclei. The parameters for the model worked out for the oxygen-containing molecules[14] were used in the present calculations without changes. However, it was additionally assumed that the distance of the lone electron pair from the S nucleus may vary from 0.4 to 0.8 Å.

Finally, the bonds were considered to be rigid with the following bond length parameters: (C–C) = 1.52 Å, (C–O) = 1.42 Å, (C–S) = 1.82 Å, (C–P) = 1.82 Å, (P–O) = 1.48 Å, (P–S) = 1.92 Å. As substituents R at the phosphorus atom in **4**, **5**, and **6** the hypothetical carbon atoms were used with the C–P bond distance equal to 1.8 Å. In our previous work[15] it was demonstrated that such an assumption does not effect the conformational behavior of real molecules containing the phosphoryl group.

Results of Calculations

In view of the contrasting conformational behavior of 2-phosphoryl-substituted 1,3-dithianes and 1,3-dioxanes, the main purpose of the present work was to estimate the energy difference (ΔE) between the axial and equatorial chair conformations of the heteroanes **4**–**6** or in other words to evaluate the conformational energy of a substituent, $\Delta E = E^{ax} - E^{eq}$. Therefore, neglecting detailed properties of the potential surface and the possible conformational interconversion pathways, the minimization of energy of the molecules 4–6 was carried out only for the axial and equatorial position of the phosphoryl and thiophosphoryl group on a chair conformation of the heterocyclic rings.

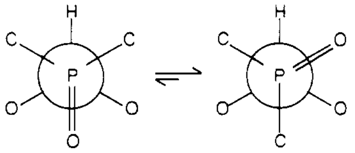
The energy minimization of the 2-phosphoryl-substituted 1,3-dioxane 4 showed that the chair conformation with the equatorial phosphoryl group is more stable than the axial one by ca. 7 kJ/mol. The primary reason for the lower stability of the axial conformation 4-ax is the increase of E^{ax} due to repulsive nonbonding 1,3-syn-axial interactions between the phosphoryl group and the methylene groups in the ring. These interactions are stronger than the energy of interactions between the lone electron pairs on endocyclic oxygens and the phosphoryl oxygen atom in the equatorial conformation 4-eq. In other words $E_{nb}{}^{ax} > E_{lep}{}^{eq}$.



4-eq **4**-ax

ΔE = 7 kJ/mol

However, the lone pair interactions are responsible for a lower energy of the equatorial conformer, 4-eq, with the gauche orientation of the phosphoryl group in respect to hydrogen on C-2. In this rotamer one of the two repulsive interactions between the lone electron pairs on the phosphoryl and ring oxygen atoms is avoided. The energy difference between anti and gauche rotamers of 4-eq was calculated as 5.5 kJ/mol.



anti **4**-eq gauche **4**-eq

ΔE = 5.5 kJ/mol

The net result is that the effective size of the axial R$_2$P(O) substituent in 4 has a decisive effect on the *E*

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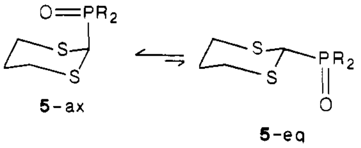
value. Moreover, whereas the geometrical parameters of the six-membered 1,3-dioxane ring are only slightly changed under the disturbing influence of the equatorial phosphoryl group, in the axial conformation, **4**-ax, the bond angles around the carbon atoms deviate by the mean value of 1.5° and the COC bond angle is enlarged to 113°. The values for the torsional angles in the ring for both **4**-ax and **4**-eq vary from 51° to 58°.

Similar calculations performed for 2-phosphoryl-substituted 1,3-dithiane (**5**) revealed an entirely different picture. In this case, the axial conformation, **5**-ax, was calculated to be more stable than the equatorial one by 5.5–8.0 kJ/mol. The range given for the E value is connected with the imprecision in the chosen parameters for the lone electron pairs on sulfur. According to calculations, the values of $E_{\text{lep}}^{\text{eq}}$ are almost the same for the 1,3-dioxane **4** and 1,3-dithiane **5**. However, due to the relatively long bond lengths between carbon and sulfur in the latter ring, there are essentially no 1,3-syn-axial repulsive interactions in the axial conformation **5**-ax. Therefore, in the case of 1,3-dithiane **5** $E_{\text{lep}}^{\text{eq}}$ is greater than $E_{\text{nb}}^{\text{ax}}$, which results in better stability and consequently in overwhelming population of the axial conformation. In other words, due to the longer C–S bond distances in **5** the effective size of the axial phosphoryl group has no influence on the E value. The conformational equilibrium of **5** is mainly determined by the interactions of the lone electron pairs of the ring and phosphoryl oxygens. Since this energy term undergoes slow changes as compared with E_{nb}, the ring geometrical parameters in both conformations **5**-ax and **5**-eq are not distinguishable.



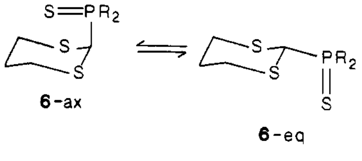
5-ax

5-eq

ΔE = 5.5–8.0 kJ/mol

In this case, the energy for the rotamer *anti*-**5**-ax was only calculated in view of the fact that this rotamer is stabilized by an attractive electrostatic interaction of the phosphoryl oxygen atom and hydrogens on C-4 and C-6 ($P{=}O^{\delta-}\cdots H_{4,6}$).[4a,8] The energy of the latter effect was, however, not taken into account in the present calculations.

Finally, calculations for **6** indicated that the replacement of the phosphoryl group by the thiophosphoryl group, which has a greater effective size (S vs O) and longer P=S bond length in comparison with P=O, leads to approximately the same population of both conformations **6**-ax and **6**-eq. The calculations showed the increased 1,3-syn-axial interactions (~4 kJ/mol) in **6**-ax and a decreased contribution of the $E_{\text{lep}}^{\text{eq}}$ (~3 kJ/mol) in **6**-eq. The latter effect is due to a relatively large distance between the ring sulfur atoms and the thiophosphoryl sulfur atom.



6-ax

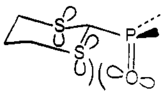
6-eq

$\Delta E \simeq 0$ kJ/mol

Discussion

The results of calculations presented above on the conformational stability of 1,3-heteroanes **4-6** are fully consistent with the experimental observations so far collected. First of all, the calculations showed that the conformational preferences of the 2-phosphoryl group in 1,3-dioxane and 1,3-dithiane rings are opposite; that is, whereas in the former it prefers an equatorial position, in the latter the favorable position is an axial one. Moreover, the calculations revealed the main reasons for this contrasting conformational behavior.

In general, the conformational preference of an organophosphorus substituent in the anomeric position of 1,3-heteroane ring is determined by three main factors: (a) the steric effect (1,3-syn axial interactions), (b) the bond lengths between the ring heteroatoms and the anomeric carbon atom, and (c) the interactions of the lone electron pairs on the ring heteroatoms with the lone electron pairs of the P substituent attached to the anomeric carbon atom. In the case of the phosphoryl group the oxygen lone electron pairs are involved in this type of interactions. The latter effect, which to the best of our knowledge has been overlooked in considerations of the origin of the anomeric effect, plays an important role in 2-substituted 1,3-dithianes where the steric interactions are greatly decreased due to extended C–S bonds.



It should be stressed that there is also a good agreement between the calculated and experimental data.[7,8] Thus, the equilibration experiments of diastereomeric 2-phosphoryl-5-*tert*-butyl-1,3-dithianes **2** led to the $-\Delta G^0$ values equal to 4.92 kJ/mol for R = MeO and 3.93 kJ/mol for R = Ph. Both of them are close to the calculated one for **5**.

Another striking result of the above calculations is the correct prediction of the gauche orientation of the phosphoryl group in the equatorial conformation of 1,3-dioxane **4**. Our recent X-ray analysis of 2-(diphenylphosphinoyl)-5,5-dimethyl-1,3-dioxane (**3**)[9a] showed that it is, indeed, the case experimentally found in the solid phase.

It is also evident from the above calculations as well as from the experimental data that the $n_S \rightarrow \sigma^*_{C-P}$ conjugation, the stereoelectronic effect, deemed primarily responsible for the anomeric effect, does not play an important role in determining the conformational stabilities of 2-substituted 1,3-dithianes. The same conclusion was reached recently by Anet and Kopelevich,[16] who investigated the conformational preferences of 2-deuterio-substituted 1,3-heteroanes.

We believe that the lone pair interactions may also be responsible for the axial preference of the carbonyl group bonded to the anomeric carbon atom in polythianes.[5k] Interestingly, in the 1,3-dioxane ring, the carbonyl group, like the phosphoryl group, prefers to be equatorial.

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