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# Conformational analysis of *p*-X-anilino dioxaphosphinanes. Substituent effects on $^{31}P$ and $^{15}N$ NMR signals and on negative hyperconjugation (n–σ*)

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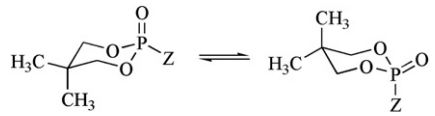
ABSTRACT

The conformational analysis of anancomeric cis-ax and cis-eq 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinanes (X=$OCH_3$, $C_6H_{11}$, H, Cl, CN and $NO_2$) is informed. In accordance with $^3J_{HH}$, $^3J_{HP}$, $^4J_{HP}$, and $^3J_{CP}$ coupling constants the preferred conformation in solution is a chair in both series of compounds. Structural parameters obtained through X-ray diffraction studies of the series of cis-ax and cis-eq diastereomers **1**–**6**, suggest that the stabilization of the axial and equatorial diastereomers in chair conformation rely on stereoelectronic $n_\pi O–\sigma^*_{P–N}$ and $n_\pi N–\sigma^*_{P–O}$ interactions, respectively. Theoretical Kohn–Sham DFT calculations support the participation of the cited stereoelectronic interactions not only to understand the conformational behavior of these systems but also to give an explanation of the observed substituent-induced chemical shift (SCS) on $^{31}P$ and $^{15}N$ NMR signals.



## 1. Introduction

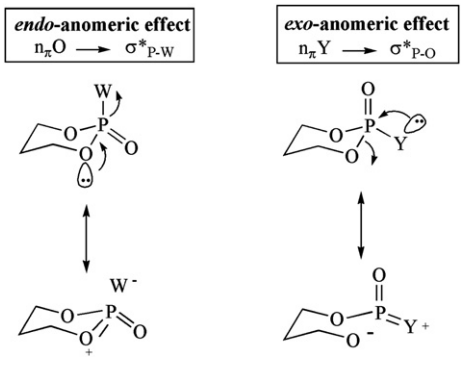
In contrast to the conformational behavior of monosubstituted cyclohexanes[1] and 2-sustituted-1,3-dioxanes,[2] where the steric effects govern the conformational preference of substituents, electronic effects play an important role in the prediction of the conformation of 1,3,2-dioxaphosphinanes.[3] For instance, in the case of the 2-*Z*-2-oxo-1,3,2λ$^5$-dioxaphosphinanes of Scheme 1, the conformational equilibrium is notably shifted to the right when *Z* is an electron withdrawing group (W) such as Cl, F or OPh;[4] or to the left when Z is an electron donating group (Y), for example, an amino substituent $NR_2$ (R=H, Me).[5]



**2-*eq*** **2-*ax***

**Scheme 1.**

This behavior has been attributed mainly to the stabilizing stereoelectronic interactions $n_\pi O–\sigma^*_{P\text{-}w(substituent)}$ (*endo*-anomeric effect) for the axial preference and the $n_\pi Y–\sigma^*_{P–Oendocyclic}$ (*exo*-anomeric effect) for the equatorial one (Scheme 2). [3a,6,7]




**Scheme 2.**

Along with the *exo*-anomeric effect, the equatorial preference of an amino group at the four-coordinated phosphorus of a 1,3,2-dioxaphosphinane ring has been ascribed to the repulsive 1,3-*syn* axial interaction between the R groups of the amino ($NR_2$)

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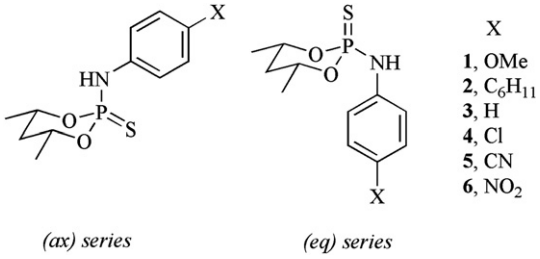
substituent and the axial hydrogen atoms at the 4 and 6 positions of the heterocycle,[3b] the stabilizing $n_{\pi}O-\sigma^{*}_{P=O(S)}$ interaction (*endo*-anomeric effect)[8] and/or the $p\pi(N)-d\pi(P)$ interaction between the lone pair at nitrogen atom and one of the empty orbitals of phosphorus.[9] However, the role played by phosphorus d orbitals in 1,3,2-dioxaphosphinanes remains controversial, and theoretical studies[10,11] performed on phosphorus compounds have provided evidence against d orbital participation even in molecules with low-lying acceptor orbitals such as those containing PO and PS groups.[12]

On the other hand, Bentrude et al. found that for analogous 2-anilino-2-oxo-5,5-dimethyl-1,3,2$\lambda^5$-oxazaphosphinanes,[13] the anilino group prefers an axial orientation in the solid state. In order to explain this observation, a stabilizing $n_{\pi N}-\sigma^{*}_{PN}$ orbital interaction, ascribed to the *endo*-anomeric effect, was proposed. From these results, it is clear that the nature of R in the amino group may change the regular tendency of the amino substituent to occupy the equatorial orientation; a tendency, that is, clearly observed, at least, in highly hindered thiophosphoramidates.[14a]

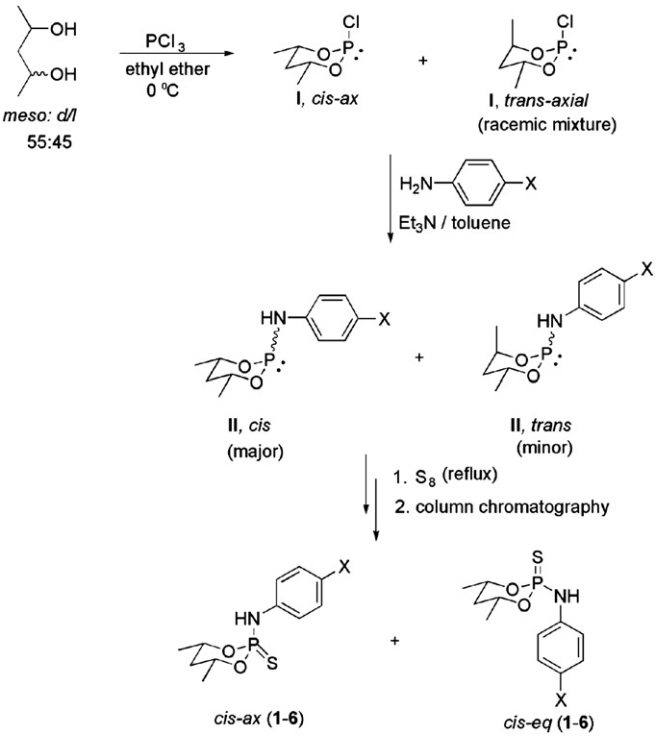
In this work we are reporting the conformational behavior of two series of anancomeric 2-anilino-1,3,2$\lambda^5$-dioxaphosphinanes (Scheme 3) in solution and in solid state. The electronic characteristics of the substituents (X) at the *para* position of the aromatic ring were varied from electron withdrawing to electron donating groups with the idea of analyzing the participation of the stereoelectronic effects in the conformation adopted by both diastereomeric series of compounds. NMR data as $^{31}P$ and $^{15}N$ chemical shifts were correlated with Hammett constants within the context of linear free-energy relationships (LFER) theory, considering that the tendencies observed are a consequence of the changes in electronic density caused by the *p*-X-substituent. Kohn–Sham DFT calculations[15] were performed to give theoretical support to the participation of $n-\sigma^{*}$ anomeric stabilization through the geometry of the optimized ground state structures.




**Scheme 3.**

## 2. Results

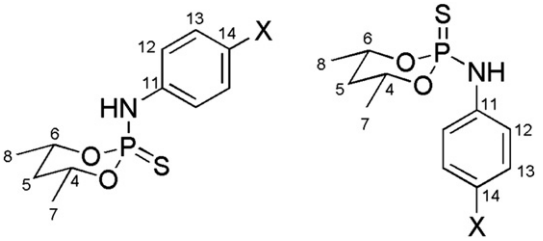
The synthesis of compounds **1**–**6** was achieved in a tandem sequence of three steps as it is summarized in Scheme 4, with the isolation of neither the intermediate 2-chloro-1,3,2-$\lambda^3$-dioxaphosphinane (**I**, mixture of isomers) nor the phosphoramidite (**II**, mixture of isomers). Both intermediates decompose with humidity; therefore, they should be managed carefully and maintained under dry atmosphere if needed (see Experimental part for details). Due to the fact that the starting 2,4-pentanediol is a mixture of *meso* and *d*/*l* isomers, thiophosphoramidates **1**–**6** were obtained as a mixture of anancomeric-cis and racemic-trans isomers. Because the first step of the synthetic pathway is diastereoselective,[16] and favors the cis-ax (**I**) over the trans-ax (**I**) isomer (the cis-eq isomer is not observed), the trans phosphoramidites (**II**) and consequently the trans thiophosphoramidates (**1**–**6**) were the minor components (10% at the most) in the mixtures cis/trans, and they were not characterized in this work. The mixture of ax and eq cis-thiophosphoramidates (**1**–**6**) was separated and purified by column chromatography.




**Scheme 4.** The nomenclature ax and eq of **1**–**6** was used to mark the position of the amino substituent, even though nitrogen ranks lower than sulfur by CIP rules.

All $^1H$ and $^{13}C$ NMR experiments were carried out in $CDCl_3$ at 27 °C. Natural abundance $^{15}N$ NMR spectra of the cis-eq series were recorded in $CDCl_3$ at 35 °C, meanwhile the cis-ax series, which are barely soluble in $CDCl_3$, were recorded in DMSO at 75 °C; the spectra were acquired with a decoupled INEPT pulse sequence ($J$=90 Hz) using nitromethane as the external reference. The assignment of configuration of cis-ax and cis-eq diastereomers was successfully attained by $^{31}P$ NMR, taking into account that the signal of the cis substituted thiophosphoramidates, is shifted to

**Table 1**
$^1H$, $^{31}P$, and $^{15}N$ chemical shifts (in ppm) for **1**–**6** ax and **1**–**6** eq 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2$\lambda^5$-dioxaphosphinanes in $CDCl_3$




| X | H4,6 | H5ax | H5eq | H7,8 | $^{31}P$ | $^{15}N$[a] |
|---|---|---|---|---|---|---|
| OMe ax | 4.64 | 1.92 | 1.79 | 1.42 | 60.6 | −298.6 |
| OMe eq | 4.84 | 1.58 | 1.76 | 1.35 | 63.5 | −295.3 |
| $C_6H_{11}$ ax | 4.65 | 1.92 | 1.79 | 1.41 | 60.0 | −295.5 |
| $C_6H_{11}$ eq | 4.87 | 1.69 | 1.81 | 1.37 | 63.0 | −291.4 |
| H ax | 4.65 | 1.93 | 1.81 | 1.44 | 59.4 | −293.8 |
| H eq | 4.88 | 1.71 | 1.82 | 1.38 | 62.9 | −290.1 |
| Cl ax | 4.62 | 1.92 | 1.80 | 1.43 | 59.4 | −293.7 |
| Cl eq | 4.87 | 1.67 | 1.82 | 1.37 | 62.9 | −290.9 |
| CN ax | 4.62 | 1.90 | 1.81 | 1.39 | 57.3 | −285.8 |
| CN eq | 4.89 | 1.75 | 1.87 | 1.36 | 62.2 | −284.5 |
| $NO_2$ ax | 4.63 | 1.93 | 1.83 | 1.43 | 57.2 | −283.8 |
| $NO_2$ eq | 4.89 | 1.78 | 1.91 | 1.41 | 61.9 | −283.6 |

[a] The $^{15}N$ spectra of cis-ax compounds were acquired at 75 °C using DMSO-$d_6$ as solvent.

high frequency of the corresponding trans isomers[12,14a] (Table 1). Proton chemical shifts ($\delta$) are reported in Table 1; the assignment of the signals and the backbone coupling constants (Table 2) were obtained through first-order analysis of the spectra, along with homo and heteronuclear decoupling experiments. The complete assignment of $^{13}C$ NMR signals (Table 3), was achieved by means of $^{1}H$, $^{13}C$ correlated 2D NMR spectra. The twelve isomers **1**–**6** are solids, thus recrystallization from mixtures of AcOEt/Hexane or $CH_2Cl_2$/Hexane rendered good quality crystals for X-ray diffraction analysis. The molecular structures are presented in Figures 1–12 and the structural parameters in Tables 1–8 (Supplementary data). The DFT calculations were carried out at B3LYP/6-31G (d,p) level of theory; such combination of exchange and correlation functional and basis set provides reliable geometries and acceptable chemical accuracy for phosphorus containing systems.[17]

**Table 2**
$^{1}H$ NMR backbone coupling constants and $^{1}J_{NP}$ (Hz) for **1**–**6** ax and **1**–**6** eq 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2$\lambda^5$-dioxaphosphinanes. First-order analysis in $CDCl_3$

| X | $^{3}J_{H4,6H5ax}$ | $^{3}J_{H4,6H5eq}$ | $^{3}J_{H4,6P}$ | $^{2}J_{H5axH5eq}$ | $^{4}J_{H7P}$ | $^{1}J_{NP}$ |
|---|---|---|---|---|---|---|
| OMe ax | 11.3 | 2.6 | 2.3 | 14.5 | 2.0 | 9.9 |
| OMe eq | 11.5 | 2.3 | 2.3 | 14.6 | 2.2 | 25.8 |
| $C_6H_{11}$ ax | 11.4 | 2.4 | 2.5 | 14.4 | 1.8 | 10.9 |
| $C_6H_{11}$ eq | 11.0 | 2.2 | 2.0 | 14.9 | 1.9 | 25.8 |
| H ax | 11.4 | 2.6 | 2.1 | 14.6 | 2.0 | 10.9 |
| H eq | 11.3 | 2.6 | 2.7 | 13.9 | 2.0 | 25.2 |
| Cl ax | 11.1 | 2.6 | 2.1 | 14.5 | 1.9 | 10.9 |
| Cl eq | 11.6 | 2.2 | 2.5 | 13.4 | 2.0 | 24.8 |
| CN ax | 11.4 | 2.6 | 2.0 | 14.6 | 1.8 | 9.9 |
| CN eq | 11.5 | 2.2 | 2.4 | 14.5 | 2.0 | 23.8 |
| $NO_2$ ax | 11.0 | 2.6 | 2.6 | 14.6 | 2.0 | 10.9 |
| $NO_2$ eq | 11.5 | 2.4 | 2.4 | 13.0 | 2.2 | 23.8 |

## 3. Discussion

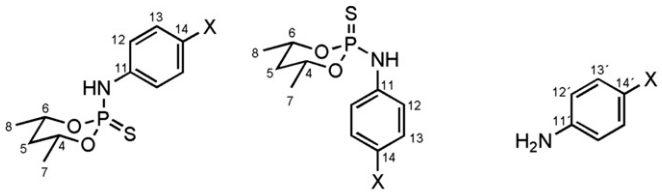
### 3.1. Conformational analysis in solution

The chemical shift of $H_{4,6}$ is in the range of 4.62–4.89 ppm (Table 1) and the corresponding of $C_{4,6}$ is in the range of 73.8–76.7 ppm (Table 3). Taking into consideration that the $C_{4,6}$ signal of the cis-ax isomers is shifted to high frequency respect to the signal of the corresponding cis-eq, but the opposite trend is found for $H_{4,6}$, it is concluded that the amino substituent of dioxaphosphinane ring suffer a reciprocal of a $\gamma_a$ *gauche* effect.[18] This effect can be ascribed to a negligible participation of the steric compression by the anilino substituent on $H_{4,6}$, very likely due to the ability of the endocyclic oxygens to change hybridization from $sp^3$ to $sp^2$ (COP angles $\sim$ 118°).[14,19]

The conformation of the dioxaphosphinane ring was deduced from vicinal coupling constants $^{3}J_{HH}$, $^{3}J_{HP}$, $^{4}J_{HP}$, and $^{3}J_{CP}$ (Tables 2 and 3). Determination of $^{3}J_{H4,6H5ax}$ and $^{3}J_{H4,6H5eq}$ was achieved through heteronuclear H{$^{31}$P} decoupling experiments, whereas $^{3}J_{HP}$ and $^{4}J_{HP}$ were obtained by direct comparison of the decoupled H{$^{31}$P} and the undecoupled $^{1}H$ NMR spectra. The observed vicinal $^{3}J_{H4H5ax}$ is around 11 Hz (*anti* arrangement) for both series of diastereomers cis-ax and cis-eq **1**–**6**, whereas $^{3}J_{H4H5eq}$ is 2.2–2.6 Hz (*gauche* arrangement), suggesting that these molecules are in solution in chair conformation. In agreement with this finding, values of $^{3}J_{H4(6)P}$ and $^{4}J_{H7(8)P}$ coupling constants are between 2.0–2.7 Hz and around 2.0 Hz, respectively.[3a,b]

On the other hand, $^{3}J_{CP}$ coupling constants obtained from $^{13}C$ NMR signals of the methyl groups at positions $C_7$ and $C_8$ for cis-ax and cis-eq, are between 8.5 and 10.8 Hz (Table 3), indicating that the molecules are in locked chair conformations.[3a,b,14] As observed initially by Nifantiev[20] for similar phosphorus heterocycles, we also found that one of the most sensible coupling constant to configuration is $^{3}J_{C5P}$; the values of the cis-ax thiophosphoramidates **1**–**6**

**Table 3**
$^{13}C$ NMR signal assignments for cis-ax and cis-eq (**1**–**6**)[a]




| *p*-X | C-4,6 ($^{2}J_{C4,6P}$) | C-5($^{3}J_{C5P}$) | C-7,8($^{3}J_{C7,8P}$) | C-11 ($^{2}J_{C11P}$)[b] | C-12 ($^{3}J_{C12P}$) | C-13 | C-14 |
|---|---|---|---|---|---|---|---|
| OMe ax | 76.0 (8.8) | 40.5 (6.2) | 22.4 (8.8) | 132.5 (n.o.) | 120.6 (6.2) | 114.8 | 155.6 |
| OMe eq | 73.8 (4.6) | 41.1 (3.1) | 22.1 (10.8) | 131.3 (5.4) | 122.6 (5.4) | 114.3 | 156.2 |
| *OMe A*[c] | — | — | — | 140.3 | 116.2 | 114.9 | 152.8 |
| $C_6H_{11}$ ax | 75.9 (9.2) | 40.5 (6.1) | 22.4 (9.2) | 137.0 (n.o.) | 118.2 (6.9) | 127.8 | 142.3 |
| $C_6H_{11}$ eq | 74.0 (4.6) | 41.2 (3.1) | 22.2 (10.8) | 136.3 (4.6) | 119.3 (6.1) | 127.5 | 142.9 |
| $C_6H_{11}$-*A*[c] | — | — | — | 144.4 | 115.4 | 127.6 | 138.5 |
| H ax | 76.0 (9.2) | 40.5 (5.4) | 22.4 (9.2) | 139.5 (n.o.) | 118.2 (6.9) | 129.4 | 122.4 |
| H eq | 74.0 (5.3) | 41.2 (3.1) | 22.1 (10.8) | 138.7 (5.4) | 119.4 (6.1) | 129.1 | 123.0 |
| H *A*[c] | — | — | — | 146.8 | 115.3 | 129.5 | 118.6 |
| Cl ax | 76.2 (9.2) | 40.4 (6.9) | 22.4 (8.5) | 138.1 (n.o.) | 119.5 (6.1) | 129.4 | 127.7 |
| Cl eq | 74.1 (4.6) | 41.1 (2.3) | 22.1 (10.8) | 137.5 (4.6) | 121.0 (6.1) | 129.0 | 128.2 |
| *Cl A*[c] | — | — | — | 145.2 | 116.3 | 129.2 | 123.0 |
| CN ax | 75.6 (7.7) | 40.4 (6.1) | 22.3 (9.2) | 144.3 (n.o.) | 118.0 (6.1) | 133.5 | 105.5 |
| CN eq | 74.9 (4.5) | 41.6 (3.1) | 22.5 (10.8) | 143.5 (4.9) | 119.1 (7.3) | 133.8 | 106.0 |
| CN *A*[c] | — | — | — | 151.1 | 114.4 | 133.7 | 99.0 |
| $NO_2$ ax | 76.7 (9.7) | 40.4 (6.1) | 22.2 (9.2) | 146.0 (n.o.) | 117.3 (6.9) | 125.6 | 142.4 |
| $NO_2$ eq | 74.5 (4.6) | 41.3 (3.1) | 22.3 (10.8) | 144.9 (4.9) | 118.2 (7.7) | 125.3 | 142.8 |
| $NO_2$ *A*[c] | — | — | — | 152.5 | 113.4 | 126.3 | 139.2 |

[a] Chemical shifts ($\delta$) in ppm from TMS in $CDCl_3$. In parentheses $J_{CP}$ in Hz.
[b] n.o.=not observed.
[c] This work.

are 2–3 Hz larger than the cis-eq ones (Table 3). It is worth mentioning that similar values of $^{3}J_{C5P}$, were reported for analogous dioxaphosphinanes in chair conformation.[14a,21] In consort, values of $^{2}J_{C4(6)P}$ are around 4.6 Hz for the cis-eq series and between 7.7 and 9.7 Hz for the cis-ax series (see Table 3).

### 3.2. Substituent effects on $^{15}$N and $^{31}$P NMR signals

The $^{15}$N chemical shifts of the dioxaphosphinanes **1**–**6** are between −298.6 and −283.6 ppm, being the signal of the equatorial compounds shifted to high frequency of the corresponding axial epimers (Table 1). As expected, an electron releasing group in the *p*-position of the aryl group leads to a shielding effect in nitrogen nucleus and vice versa.[22] Nevertheless, the opposite behavior is observed for the $^{31}$P chemical shifts (Table 1).

In agreement with the data reported in the literature for cyclic oxazaphospholidines[23] and phosphoramidates,[24] where changes in geometry around the nitrogen atom (C–N–P bond angle mainly) explain the trend observed in $^{15}$NMR chemical shifts; we also observed by means of X-ray diffraction analysis (see below) that there is a flattening of the nitrogen edge in the case of the equatorial series, with the consequent opening of the $C_{11}$–N–P bond angle, that explains the deshielding of the $^{15}$N NMR signal. Along with this geometrical change, we found that the electronic nature of the *para* substituent influences the electronic density around the nitrogen, therefore the chemical shift. This electronic effect is observed for both axial and equatorial isomers; although it is greater for the axial series with a difference of almost 15 ppm, between the low-frequency shifted signal (X=OMe) and the high-frequency shifted peak (X=$NO_2$), whereas the corresponding difference for the equatorial series is around 12 ppm.

In order to evaluate the nature of the so-called Substituent-Induced Chemical Shifts (SCS), several plots of $\delta^{15}$N, $\delta^{31}$P, and $\delta^{13}$C (C-11) data of both series of compounds against Hammett type constants ($\sigma_p^-$ and $R^-$)[25] were performed. The regression coefficient (R) and the slope of the linear correlations for each series is presented in Table 4; acceptable regression values R∼0.98 ($\sigma_p^-$ and $R^-$) were obtained for both $^{31}$P and $^{15}$N chemical shifts. The slope of the curves is significantly higher (∼ four times for the ax series and ∼ eight times for the eq series) for the correlation of $R^-$ (or $\sigma_p^-$) vs $\delta^{15}$N than the corresponding for $R^-$ (or $\sigma_p^-$) vs $\delta^{31}$P; these results suggest that the nitrogen atom is more susceptible to sense electronic effects than the phosphorus atom, this is perhaps due to the fact that the anilino nitrogen is four bonds apart from the X substituent and phosphorus is five bonds apart; moreover, the nitrogen lone pair π-overlaps with the aromatic ring, contributing to polarization and charge redistribution by resonance effect. The slope of the curves $R^-/\delta^{15}$N for cis-ax and cis-eq compounds are 12.7 and 9.9, respectively, indicating that charge distribution is more important in the axial series than in the equatorial. Linear correlations were also performed for aniline carbons; however, only C-11 ($C_{ipso}$ to nitrogen) gave a good regression value (R ∼ 0.98) with $R^-$; the slopes of the curves $R^-/\delta$C-11 for the ax and eq series are closer to the corresponding of $R^-/\delta^{15}$N than to the corresponding of $R^-/\delta^{31}$P, as expected (Table 4). These findings give support to the participation of the stabilizing hyperconjugative *endo*-anomeric effect [$n_\pi O–\sigma^*_{P–N}$] for the axial isomers and the corresponding *exo*-anomeric effect [$n_\pi N–\sigma^*_{P–O}$] for the equatorial (see discussion below).[3,14]

In addition, it can be observed from Table 4, that $^{31}$P chemical shifts of axial and equatorial diastereomers correlate inversely with $\sigma_p^-$ and $R^-$ (average slope values: ∼ −2.58 for cis-ax, and ∼ −1.04 for cis-eq), which indicate the inverse dependence of the charge transfer from the *p*-substituent of the aryl group to phosphorus, where electron withdrawing substituents provoke a shielding effect and vice versa. We explained this abnormal behavior in an earlier study on thiophosphates[21] by proposing a charge compensation effect involving the transfer of charge from the endocyclic oxygens to phosphorus. In consort, Kuivalainen et al.[26] found by using AIM theory that it is very likely that the origin of the $^{31}$P chemical shift of *O*,*O*-dialkyl-*O*-aryl phosphorothionates relies on a back bonding character (X →P) of the P–O and P═S bonds. The variation of the chemical shift on the phosphorus nucleus can also be explained as the result of a geometrical change in the OPO bond angle of the dioxaphosphinane ring, as demonstrated by Gorenstein for cyclic and acyclic phosphates;[27] however, we did not observe significant changes in the OPO bond angle, neither within the axial series nor within the equatorial ones, of the X-ray structures of thiophosphoramidates **1**–**6**.

### 3.3. Solid state structural analysis

In order to support the participation of stereoelectronic effects in the conformation adopted for aromatic thiophosphoramidates, X-ray diffraction analyses of compounds (**1**–**6**) in cis-ax and cis-eq configurations were performed. The structure drawings are shown in Figures 1–12, and data collection and refinement parameters for the axial series and equatorial series in Tables 1 and 2, respectively (Supplementary data). Seven of the twelve compounds crystallized in the monoclinic system; the space group for cis-ax (**5** and **6**) and cis-eq (**1**, **3**, and **4**) is P21/c, whereas for cis-ax-**2** and cis-eq-**2** is P21/a, and P21/n, respectively. Four of the other five compounds [cis-ax (**1**, **3**, **4**) and cis-eq-**6**] crystallized in the triclinic system in P-1 space group; and the last one, the cis-eq-**5**, crystallized in the Pbca space group of the orthorhombic system. Two molecules per unit cell were found for six compounds: cis-ax and cis-eq (**1**, **3**, and **4**), with basically the same dioxaphosphinane ring conformation in each pair, but changes in the rotameric conformation of the anilino substituent. Selected bond lengths, bond angles and torsion angles are presented in Tables 3–8 (Supplementary data). The N–H hydrogen atom of all the structures was located from a difference Fourier map and refined.

In agreement with the conformation adopted by the molecules in solution, the dioxaphosphinane ring, of the twelve crystalline structures, is in the chair conformation. In the case of the equatorial series; regardless of the electronic nature of the *p*-X-substituent, the rotameric conformation of the anilino group (P–N bond

**Table 4**
Linear correlations between NMR parameters and Hammett constants

| **1**–**6** cis-ax compounds | | | | **1**–**6** cis-eq compounds | | | |
|---|---|---|---|---|---|---|---|
| x | y | $R^a$ | Slope | x | y | $R^a$ | Slope |
| $\sigma_p^-$ | $\delta^{31}$P | 0.984 | −2.145 | $\sigma_p^-$ | $\delta^{31}$P | 0.976 | −0.858 |
| $R^-$ | $\delta^{31}$P | 0.977 | −3.024 | $R^-$ | $\delta^{31}$P | 0.975 | −1.215 |
| $\sigma_p^-$ | $\delta^{15}$N | 0.988 | 8.989 | $\sigma_p^-$ | $\delta^{15}$N | 0.957 | 6.709 |
| $R^-$ | $\delta^{15}$N | 0.981 | 12.665 | $R^-$ | $\delta^{15}$N | 0.993 | 9.879 |
| $\sigma_p^-$ | $\delta^{13}$C (C-11) | 0.939 | 7.310 | $\sigma_p^-$ | $\delta^{13}$C (C-11) | 0.930 | 7.241 |
| $R^-$ | $\delta^{13}$C (C-11) | 0.989 | 10.901 | $R^-$ | $\delta^{13}$C (C-11) | 0.984 | 10.881 |

[a] Regression coefficient values.

rotation) is in close proximity in all cases: $\omega_{O-P-N-C11}$ spans a range of approximately 37–71° and $\omega_{S-P-N-H10}$ of 1–22° (Table 8, Suppl. Mat.), provided that the hybridization of the nitrogen atom is nearly $sp^2$ (see below). The plane of the aromatic ring (N–C11 bond rotation) tend to be parallel to the bisector plane of the dioxaphosphinane ring ($\omega_{C12-C11-N-H10}$ ~7–33° and $\omega_{C12-C11-N-P}$ ~132–178°); this rotameric conformation allows some delocalization of the nitrogen lone pair, into the aromatic ring by π-resonance; considering that the ideal delocalized structure is expected to have $\omega_{C12-C11-N-H10}$=0° and $\omega_{C12-C11-N-P}$=180°. The situation in the axial series is similar, taking into account that all diastereomers have close rotameric (P–N) conformations; the hydrogen of the N–H group is pointing toward one of the endocylic oxygens [$\omega_{O1(3)-P2-N10-H10}$ ~21–27°, $\omega_{O3(1)-P2-N10-H10}$ ~132–137°, $\omega_{S9-P2-N10-H10}$ ~94–105°] (Table 7, Suppl. Mat.). Even though this conformation suggests the existence of an intramolecular [N–H···O] hydrogen bond [N–O bond distance is around 2.51 Å (average value) against 2.75–3.0 Å obtained from the van der Waals radii sum],[28] the [N–H···O] geometry is not proper for the non-covalent interaction (82°, average); thus, the H···O distance is 2.45 Å (average), far from the observed 2.0 Å in the case of a hydrogen bond.[29] Here again the nitrogen has a nearly $sp^2$ hybridization (see below), and the aromatic ring is located outside the dioxaphosphinane ring avoiding, this way, the 1,3-syn axial steric compression with the axial hydrogen atoms at the C4 and C6 positions. The preferred rotational N–C11 conformer of the axial compounds is such, that it is clearly benefited of delocalization of the *N*-lone pair within the aromatic ring ($\omega_{C12-C11-N-H10}$ ~173–179° and $\omega_{C12-C11-N-P}$ ~15–24°).

The geometry around the phosphorus atom for the equatorial as well as for the axial diastereomers, is tetrahedral; the sum of the four angles around P is in the range of 439.38–440.19 degrees for the ax series and 434.5–436.33 degrees for the eq series (Tables 5 and 6), giving rise to a mean tetrahedral angle of 109.9° for the ax dioxaphosphinanes and108.8° for the eq series. On the other hand, the sum of the angles around the nitrogen atom is close to 360°, within the interval of 354.05° to 357.9° for the axial series (excluding cpd. cis-ax-**2** whose value: 359.71° is off of the mean value) and 357.3° to 360.8° for the equatorial series (excluding cpd. cis-eq-**6** whose value: 355.3° is off of the mean value), showing that the geometry at the nitrogen atom is almost planar (mean trigonal angle of 118.66° for the ax and 119.68° for the eq cpds., Tables 5 and 6). These findings are in agreement to those reported for analogous thiophosphoramidates,[14] where the nitrogen atom of the equatorial isomers tends to be flatter than the nitrogen of the axial ones. Consequently, the changes in nitrogen $sp^2$ hybridization between the two series of compounds, are in favor of an increase in s-character of the equatorial P–N bond with respect to the axial P–N bond, that according to Stec rule[30] accounts for the observed increase in $^1J_{PN}$ coupling constant for the equatorial thiophosphoramidates **1**–**6** [i.e., $^1J_{PN}$ (eq) ~25 Hz vs $^1J_{PN}$ (ax) ~10 Hz, Table 2]. Interestingly, the geometrical differences in nitrogen hybridization may also explain the deshielding of the equatorial $^{15}$N NMR signal as compared to the axial [i.e., $\Delta\delta^{15}$N(eq-ax), X: OMe=3.3; $C_6H_{11}$=4.4; H=3.7; Cl=2.8; CN=1.3; $NO_2$=0.2 Hz] since as it was pointed out by Gray,[24] the change in the pyramidal like ($sp^3$) nitrogen to trigonal ($sp^2$), is accompanied by a substantial

**Table 5**
Structural properties of cis-ax **1**–**6**

| Molecule A/B | **1**a | **2**a | **3**a | **4**a | **5**a | **6**a |
|---|---|---|---|---|---|---|
| Geometry at phosphorus[a] | 439.89 | 440.01 | 439.89 | 440.19 | 439.38 | 439.46 |
| | 439.92 | | 439.96 | 440.08 | | |
| Geometry at nitrogen[b] | 356.83 | 359.71 | 356.60 | 356.22 | 357.25 | 354.05 |
| | 355.91 | | 357.90 | 356.68 | | |
| Baeyer strain[c] | 112.25 | 112.16 | 112.49 | 112.54 | 112.46 | 112.47 |
| | 112.37 | | 112.41 | 112.62 | | |
| Pitzer strain[d] | 52.16 | 52.50 | 51.30 | 51.17 | 51.52 | 51.45 |
| | 51.78 | | 51.68 | 50.68 | | |
| cos ω | 0.61 | 0.61 | 0.63 | 0.63 | 0.62 | 0.62 |
| | 0.62 | | 0.62 | 0.63 | | |
| $-\cos\theta/(1+\cos\theta)$ | 0.61 | 0.61 | 0.62 | 0.62 | 0.62 | 0.62 |
| | 0.62 | | 0.62 | 0.63 | | |

[a] Calculated as the sum of the bond angles (O1P2O3), [OP2N10 (mean)], [OP2S9 (mean)], and (S9P2N10) in deg.
[b] Calculated as the sum of the bond angles (P2N10C11), (P2N10H10), and (C11N10H10) in deg.
[c] Calculated as the average value of the bond angles (O1P2O3), (O1C6C5), (O3C4C5), (C4O3P2), (C6C5C4), and (C6O1P2) in deg.
[d] Calculated as the average absolute value of the torsion angles (O1P2O3C4), (O1C6C5C4), (O3P2O1C6), (O3P2O1C6), (P2O3C4C5), and (P2O1C6C5) in deg. (For single angle values, see Tables 5 and 7 in supplementary Data).

**Table 6**
Structural properties of cis-eq **1**–**6**

| Molecule A/B | **1**e | **2**e | **3**e | **4**e | **5**e | **6**e |
|---|---|---|---|---|---|---|
| Geometry at phosphorus[a] | 434.50 | 435.77 | 435.75 | 436.0 | 436.33 | 435.82 |
| | 436.09 | | 435.74 | 435.78 | | |
| Geometry at nitrogen[b] | 358.15 | 359.90 | 360.80 | 357.50 | 359.41 | 355.30 |
| | 358.63 | | 359.20 | 357.30 | | |
| Baeyer strain[c] | 111.19 | 111.76 | 110.86 | 111.13 | 111.17 | 111.94 |
| | 111.68 | | 111.56 | 111.80 | | |
| Pitzer strain[d] | 55.50 | 53.98 | 56.59 | 54.59 | 55.76 | 53.50 |
| | 54.09 | | 54.66 | 54.62 | | |
| cos ω | 0.57 | 0.59 | 0.55 | 0.58 | 0.56 | 0.59 |
| | 0.59 | | 0.58 | 0.58 | | |
| $-\cos\theta/(1+\cos\theta)$ | 0.57 | 0.59 | 0.55 | 0.56 | 0.56 | 0.60 |
| | 0.58 | | 0.58 | 0.59 | | |

[a] Calculated as the sum of the bond angles (O1P2O3), [OP2N10 (mean)], [OP2S9 (mean)], and (S9P2N10) in deg. .
[b] Calculated as the sum of the bond angles (P2N10C11), (P2N10H10), and (C11N10H10) in deg.
[c] Calculated as the average value of the bond angles (O1P2O3), (O1C6C5), (O3C4C5), (C4O3P2), (C6C5C4), and (C6O1P2) in deg.
[d] Calculated as the average absolute value of the torsion angles (O1P2O3C4), (O1C6C5C4), (O3P2O1C6), (O3P2O1C6), (P2O3C4C5), and (P2O1C6C5) in deg. (For single angle values, see Tables 6 and 8 in supplementary data).

deshielding, at least in heterocyclic phoshoramidates. Besides; as it was pointed out earlier, the SCS correlations found for nitrogen atom, indicates that the chemical shifts are also sensible to electronic effects of the *p*-substituent transmitted not only by inductive but also by resonance effects. This can also be observed by the fact that the list of values of $\Delta\delta^{15}$N(eq-ax) just mentioned above, is not a constant value, but it tends to decrease as the electron withdrawing characteristic of the *p*-substituent is increased. We will come back to this point in the discussion below.

Summarized in Tables 5 and 6, are also the Baeyer and Pitzer strain [calculated as the average of the internal bond angles ($\theta$), and torsion angles ($\omega$) of the dioxaphosphorinane ring, respectively], for all the crystalline compounds. The agreement between the values obtained through the formulas cos $\omega$ and $-\cos\theta/(1+\cos\theta)$ has been employed in our group,[14,21] in analogous systems, as an indication of the propensity of the dioxaphosphorinane ring in chair conformation to establish the same compromise between averaged ring torsional and angular strain that the one existing in cyclohexane in chair conformation.[31] As observed in Table 5, the values of these parameters, obtained for the axial series are close to 0.62 with discrepancies of not more than $\pm$0.01 unity for each pair. On the other hand; in the equatorial series (Table 6), both strain values do not average to a single value, but to an interval of 0.55–0.60; however, here again the discrepancies between every pair of values are negligible ($\pm$0.01 to $\pm$0.02).

Taking into consideration that the Internal (I) strain in a heterocyclic molecule is modified by changes from $sp^3$–$sp^2$ hybridization of one or more than one of the atoms in the ring,[32] we consider pertinent to analyze the differences in Baeyer strain between the eq and ax compounds taking as reference the tetrahedral angle (109.5°) and 60° for the minimum Pitzer strain. Substituting these values in the strain formulas cos $\omega$ and $-\cos\theta/(1+\cos\theta)$, both become 0.5; thus we conclude that the equatorial diastereomers have less geometrical ring strain, than the axial ones, since the strain values of the eq compounds are closer to 0.5. Thus, Baeyer and Pitzer cos values by themselves can give a clue on the origin of the conformational effects. It is important to remark, that when the Baeyer and Pitzer strain for a molecule compromise within themselves, it can be assumed that the strain of the molecule is minimized in chair conformation. However, if this is not the case, the ring conformation is distorted to a twist or boat as in highly crowded thiophosphoramidates.[14]

On the other hand, in some cases an anilino group in phosphorus containing heterocycles, prefers an axial conformation;[33] therefore, a simple analysis based on ring strain is not sufficient to explain the observed conformational effects. Indeed, it has been demonstrated, several times, that the conformation adopted by 1,3,2-dioxaphosphinanes is highly dependent on stereoelectronic effects as we have already mentioned in the introduction of this work. We will address this point in the next section.

On the other hand, we found that the dioxaphosphinane ring is an irregular chair, since the OPO region tend to be flat as a result of the nearly planar $sp^2$ hybridization of the oxygen atoms [ax $\theta_{COP}$ (average), X: OMe 118.42°, $C_6H_{11}$ 117.88°, H 118.76°, Cl 118.92°, CN 118.43°, $NO_2$ 118.48°; eq $\theta_{COP}$ (average), X: OMe 117.0°, $C_6H_{11}$ 118.29°, H 116.5°, Cl 117.15°, CN 116.46°, $NO_2$ 118.15°]. As observed, with the exception of the thiophosphoramidate **2** (X=$C_6H_{11}$), the COP bond angles are larger for the axial than for the equatorial compounds; this tendency could be explained invoking a possible 1,3-*syn* axial compression of the aniline group with the hydrogens at C4 and C6 in the axial isomers; however, the fact that the tendency is reverted for the most crowded compound **2**, is not supporting this hypothesis. Alternatively, the opening of the COP bond angle for the ax isomers can be explained through the participation of the stabilizing stereoelectronic $n_\pi O$–$\sigma^*_{P-NAr}$ effect, as discussed below.

### 3.4. Stereoelectronic effects

According to Deslongschamps,[34] a stereoelectronic effect is observed in a molecule when the spatial disposition of a $\pi$ donor electron pair (bonded or non bonded), is antiperiplanar to the acceptor $\sigma^*$ antibonding orbital. This effect is customarily described as *negative hyperconjugation* or as *generalized anomeric effect* (term used to denote the axial preference of an electronegative substituent over the equatorial, in the anomeric position of a pyranose sugar ring). On the other hand, the term *reverse anomeric effect* is used when a cationic substituent at the anomeric position of a pyranose sugar, shifts the equilibrium toward the equatorial anomer.[7c,35]

In the conformational analysis of highly crowded 2-dicyclohexylamino-2-thio-1,3,2-dioxaphosphinanes (structure A, Fig. 1), we have observed that negative hyperconjugation of the type n–$\sigma^*$, is as important as the van der Waals steric compression, to drive the conformational preference of the amino substituent, in a mobile system, to occupy the equatorial position.[14] However, in analogous 2-anilino-2-oxo-1,3,2-oxazaphosphinanes (structure B, Fig. 1), where the amino substituent is clearly more electronegative, the axial conformer is in preference over the equatorial; Bentrude et al.,[33a] have interpreted the axial preference of the anilino substituent in terms of an *endo*-anomeric (n–$\sigma^*$) stereoelectronic interaction. These results are in agreement with the stereoelectronic interactions found in protonated glucosylanilines where a more localized positive charge on nitrogen leads to a decrease in the reverse anomeric effect.[35] Therefore, we can deduce that negative hyperconjugation is likely to be in operation not only in the equatorial but also the axial series of anancomeric thiophosphoramidates (**1**–**6**). In this section, we examine the influence of the electronic effect of the *p*-X-substituent on the geometry and conformation adopted by the molecules in solid state and in gas phase through the geometries obtained by means of theoretical Kohn–Sham DFT calculations.[15] Considering that the stabilization of a ring conformation by anomeric n–$\sigma^*$ effect, implies the participation of a double bond–no–bond structure in resonance with its normal *lewis* formula (see examples in Scheme 2), we certainly expect to have shortening or lengthening of vicinal phosphorus bonds, along with an opening of the COP bond to almost 120°.

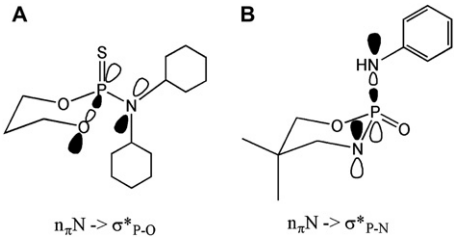


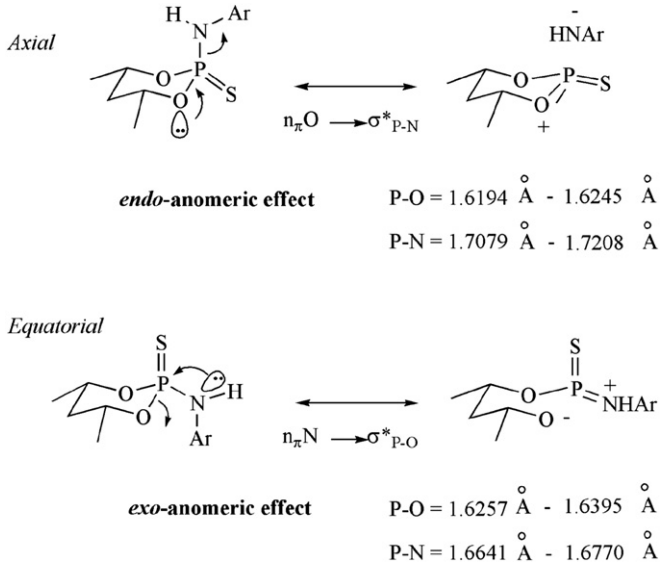

**Figure 1.** Negative hyperconjugation in six-membered ring phosphorus compounds.

The chair conformation adopted by the axial and equatorial thiophosphoramidates **1**–**6** in gas phase, was not destabilized by modifying the electronic nature of the *p*-X-substituent; however, variation in geometry, specifically bond lengths of vicinal P–O, P–N and P–S bonds, indeed varied periodically with the change of the X group (see Table 7); giving support to the participation of hyperconjugation, as the main mechanism of stabilization of thiophosphoramidates.

As it was mentioned before the hybridization on oxygens is closer to $sp^2$ than to $sp^3$,[36] and as observed in Table 7, the endocyclic O1–P bond lengths are smaller in the axial series than in the equatorial, but the opposite trend is found for the N–P bond lengths. These tendencies are in agreement with the shortening and lengthening expected for the *endo*-anomeric $n_\pi O$–$\sigma^*_{P-N}$ interaction operating in the cis-ax series, and the *exo*-anomeric $n_\pi N$–$\sigma^*_{P-O}$ interaction operating in cis-eq series, as summarized in Scheme 5.

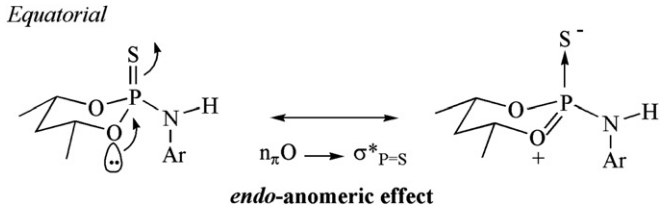
**Table 7**
Selected bond distances (Å) for cis-ax **1**–**6** and cis-eq **1**–**6** at B3LYP level of theory with the basis set 6-31G (d,p)

| | O1-P | O3-P | N-P | P-S | N-C11 |
|---|---|---|---|---|---|
| OMe ax | 1.6244 | 1.6245 | 1.7079 | 1.9274 | 1.4226 |
| OMe eq | 1.6395 | 1.6292 | 1.6641 | 1.9452 | 1.4262 |
| $C_6H_{11}$ ax | 1.6230 | 1.6245 | 1.7090 | 1.9269 | 1.4187 |
| $C_6H_{11}$ eq | 1.6316 | 1.6279 | 1.6643 | 1.9448 | 1.4196 |
| H ax | 1.6226 | 1.6238 | 1.7093 | 1.9264 | 1.4172 |
| H eq | 1.6315 | 1.6278 | 1.6654 | 1.9441 | 1.4186 |
| Cl ax | 1.6219 | 1.6224 | 1.7127 | 1.9253 | 1.4143 |
| Cl eq | 1.6272 | 1.6272 | 1.6685 | 1.9426 | 1.4163 |
| CN ax | 1.6197 | 1.6204 | 1.7180 | 1.9237 | 1.4054 |
| CN eq | 1.6281 | 1.6256 | 1.6740 | 1.9401 | 1.4058 |
| $NO_2$ ax | 1.6194 | 1.6196 | 1.7208 | 1.9224 | 1.4022 |
| $NO_2$ eq | 1.6258 | 1.6257 | 1.6770 | 1.9392 | 1.4014 |




**Scheme 5.**

The averaged values of the P–O and P–N bond distances in the X-ray structures (Tables 3 and 4, Suppl. Mat.) are smaller than the theoretical ones; however, they follow the same trend: ax series [(P–O) 1.5661–1.5821 Å, and (P–N) 1.6479–1.6632 Å]; eq series [(P–O) 1.561–1.587 Å, and (P–N) 1.619–1.643 Å]. The small differences in P–O bond lengths between the ax and eq isomers are perhaps due to the participation of the second stabilizing anomeric interaction: $n_\pi O–\sigma^*_{P=S,}$ in operation in the eq isomers (Scheme 6). This interaction is also supported by the lengthening of the P–S bond of the equatorial compounds as compared to the axial [$(P–S)_{ax}$ 1.9224 –1.9274 Å vs $(P–S)_{eq}$ 1.9392 –1.9452 Å] (Table 7). It is worth of mention that similar *endo*-anomeric $n_\pi O–\sigma^*_{P=X}$ (X=O, S) effect has been proposed as plausible, although not strong stabilizing interaction, in analogous 2-substituted-1,3,2λ$^5$-dioxaphosphinanes.[8]




**Scheme 6.**

The influence of the *p*-substituent at the aniline ring, in the stabilization of the anancomeric thiophosphoramidates **1**–**6**, can be analyzed through two factors: (a) a field/inductive effect, and (b) a resonance effect. From a comparison of the regression values of Hammett type linear correlations with the constants ($\sigma_p^-$ or $R^-$) and $\delta^{13}C$ (C-11) (Table 4); we deduced, that the resonance effect ($R^-$) may have more importance than the field/inductive effect (taken into consideration in $\sigma_p^-$, as a combined effect) in the propagation of the electronic density from a donor substituent to any of these nuclei; or vice versa, for an attractor substituent. Taking this into account, and considering that stereoelectronic interactions are largely dependent on charge distribution of polar groups in the molecule, we analyze the resonance effect of the *p*-substituent (donor or acceptor) in the stabilization by negative hyperconjugation (n–σ*) of axial and equatorial thiophosphoramidates **1**–**6**, through the transquinoidal mesomeric structures C and D that are the result of the π-conjugation of the nitrogen electronic charge into the aromatic ring in the two tautomeric structures A↔B depicted in Figures 2 and 3.

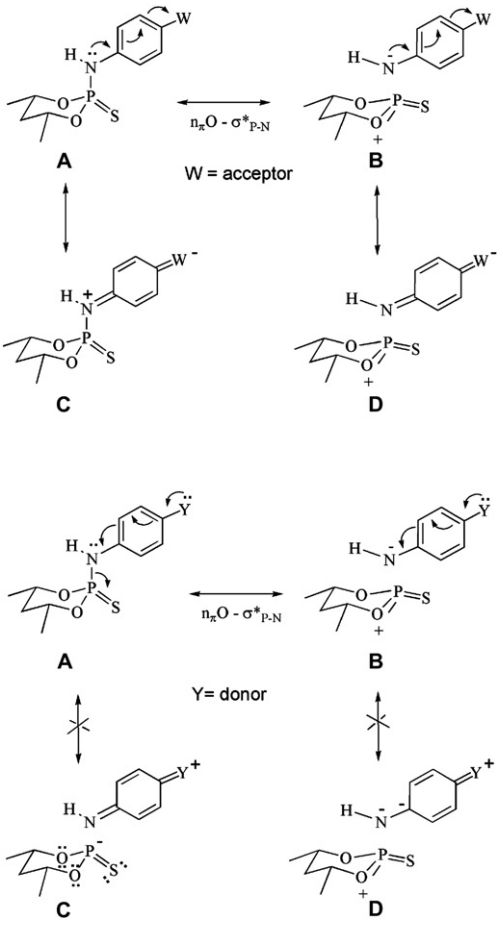



**Figure 2.** Resonance effects of *p*-substituents and negative hyperconjugation (axial series).

In the axial series (Fig. 2), structures C and D (for an acceptor group), certainly stabilize the hyperconjugative A and B structures. However, C and D (for a donor group) do not accomplish the same goal, because neither structure C nor D are stabilized; in C the phosphorus atom can not bear the lone pair in axial position because the vicinal oxygens have lone pairs in antiperiplanar relationship to the first, which is highly unstable; whereas in D there are two negative charges in neighboring atoms. In short, because of the participation of the *endo*-anomeric $n_\pi O–\sigma^*_{P–N}$ interaction, the mesomeric C and D structures help to stabilize the axial (*p*-W-anilino) substituents but not the axial (*p*-Y-anilino) substituents; and this hypothesis can be proved through the extent at which

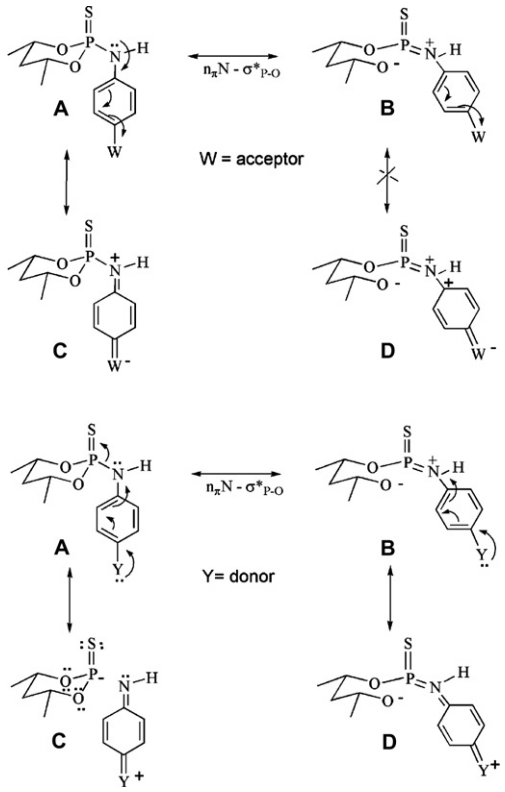



**Figure 3.** Resonance effects of *p*-substituents and negative hyperconjugation (equatorial series).

shortening of the endocyclic P–O bonds and lengthening of the exocyclic P–N bond is taking place. Indeed, we found shorter P–O bonds accompanied with longer P–N bonds for thiophosphoramidates with electron withdrawing (W) substituents than for those with electron releasing (Y) substituents [i.e., P–O bond length: ($NO_2$) 1.5708 Å (average) vs (OMe) 1.5757 Å (average); P–N bond length ($NO_2$) 1.6632 Å vs (OMe) 1.6493 Å (average) (Table 3, Suppl. Mat.), and the same tendency can be observed in theoretical bond lengths in Table 7]. On the other hand, in the equatorial series (Fig. 3) an acceptor W group is not of help for the *exo*-anomeric $n_{\pi}N–\sigma^*_{P–O}$ interaction because of two reasons: one is that the lone pair on the nitrogen atom needed for the stereoelectronic interaction is distracted in the conjugation with the π-electron density of the aniline ring (structure C); and the other is, that the mesomeric structure D is not stable because it has two positive charges in neighboring atoms. Nevertheless, a donor Y group indeed stabilizes the structures A and B by resonance with C and D, respectively; because in C, the lone pair on phosphorus in the equatorial position is stabilized by *gauche* effect;[37] and in D, the positive charge is delocalized in the aromatic ring. Here again, the shortening of the exocyclic P–N bond and lengthening of the endocyclic P–O bond for the thiophosphoramidates with donor substituents as compared to the acceptors, can be taken as a proof of the participation of the *exo*-anomeric effect [i.e., P–N bond length: (OMe) 1.621 Å (average) vs ($NO_2$) 1.640 Å P–O bond length (OMe) 1.5814 Å (average) vs ($NO_2$)1.583 Å (average) (Table 8, Suppl. Mat.)]. Although the P–O bond length difference in X-ray is not very clear; the theoretical values sustain the hypothesis [P–N bond length: (OMe) 1.6641 Å vs ($NO_2$) 1.6770 Å P–O bond length (OMe) 1.6344 (average) Å vs ($NO_2$)1.6258 Å (average) (Table 7)]. From the above results, one can confirm that the *p*-X-substituent have the main electronic influence in the negative hyperconjugation stabilization of the dioxaphosphinane ring (in both ax and eq configurational isomers **1**–**6**), through the conjugation of the nitrogen lone pair with the π-electrons of the aromatic aniline ring. This conjugation is more important in the ax series than in the eq series, as confirmed by the larger differences found in N–C11 bond length between cpd. cis-ax-**6** with an acceptor ($NO_2$) group and cpd. cis-ax-**1** with a donor (OMe) substituent as compared with the corresponding cis-eq compounds [ax: ($NO_2$) 1.396 Å vs (OMe) 1.417 Å (average); eq: ($NO_2$) 1.426 Å (OMe) 1.424 Å (average)] (Tables 11 and 12, Suppl. Mat.).

Besides, the electronic behavior of the aniline ring carbons (C-11 to C-14) was analyzed through the linear correlations between $\delta^{13}C$ of the thiophosphoramidates **1**–**6** and the $\delta^{13}C$ of the *p*-substituted anilines (Table 9, Suppl. Mat.), whose chemical shifts were determined in this work and are summarized in Table 3. As observed in Table 9, slight deviations of an ideal linear correlation (slope=1), were observed for C-11 and C-13 chemical shifts for both series of compounds. Carbon-11 of the thiophosphoramidates is shifted to low frequencies of the corresponding anilines by around 8 ppm (Table 3), indicating that the dioxaphosphinane ring behaves as an electron donating inductive group toward the aniline moiety. The regression coefficient for the curve $\delta^{13}C12/\delta^{13}C12'$ is poor for both series (∼ 0.85) and the corresponding for $\delta^{13}C14/\delta^{13}C14'$ is not very good (∼ 0.96) (Table 9, Suppl. Mat.); the inductive effect of the substituent (electronegativity of the atom or group directly attached), is perhaps predominant in C-14.

Finally, we observed that the *endo*-anomeric $n_{\pi}O–\sigma^*_{P–N}$ interaction not only explains the structural changes (bond lengths) observed for the axial thiophosphoramidates but also the COP bond opening expected for the axial, as compared to the equatorial series [i. e. averaged COP angles: OMe (ax) 118.41 vs (eq) 117.0; $NO_2$ (ax) 118.48 vs (eq) 118.15]. In addition, this stereoelectronic interaction also gives support to the compensation of phosphorus charge from the endocyclic oxygens proposed to explain the reversal tendency observed for $^{31}P$ NMR chemical shifts in 1,3,2-dioxaphosphinanes.[21]

## 4. Conclusions

The conformational analysis of diastereomeric cis-ax and cis-eq 2-*p*-X-anilino-2-thio-4,6-dimethyl-1,3,2-$\lambda^5$-dioxaphosphorinanes (**1**–**6**) was carried on in solution and in solid state. Regardless of the *p*-X-subtituent, it was found that the preferred conformation was a chair in both series. The dioxaphosphinane ring is an irregular chair; the oxygens at the OPO region are almost planar and the phosphorus atom is a puckering end. The ability of the endocyclic oxygens to change hybridization from $sp^3$ to $sp^2$ is higher in the axial series than in the eq series; as a consequence, the steric compression caused by 1,3-*syn* axial interaction of the anilino substituent, with $H_{4,6}$ is practically negligible. The geometry around the nitrogen atom, for both series of diastereomers, is trigonal; however, the nitrogen of the equatorial isomers tends to be flatter than the nitrogen of the axial ones. This finding accounts for the observed increase in $^1J_{PN}$ coupling constants, for the eq series (Stec rule).

Substituent-Induced Chemical Shifts were evaluated and a comparison of the slope values for the correlations of $R^-$ (or $\sigma_p^-$) versus $\delta^{15}N$, $\delta^{31}P$ and $\delta^{13}C$ led to the conclusion that the electronic effect is sensed by the nitrogen atom and by C-11 more effectively than by the phosphorus atom. Meanwhile $^{15}N$ and $^{13}C$ NMR shifts have normal SCS trends, a reversal trend was found for correlations of $\delta^{31}P/\sigma_p^-$ or $\delta^{31}P/R^-$, this reversibility can be explained by charge density transfer from oxygens toward the phosphorus nuclei.

The participation of the stabilizing hyperconjugative *endo*-anomeric effect [$n_{\pi}O–\sigma^*_{P–N}$] for the axial isomers and *exo*-anomeric effect [$n_{\pi}N–\sigma^*_{P–O}$] for the equatorial isomers was confirmed by the expected shortening and lengthening of vicinal phosphorus bonds observed in the solid state structures and in the minimized ground state structures, obtained by DFT calculations.

The preferred rotational N-C11 conformer is such, that the nitrogen lone pair is conjugated with the π-electrons of the aromatic ring, contributing to polarization and charge redistribution by resonance effect; this effect is somewhat more important in the axial, than in the equatorial series.

The electronic influence of the *p*-substituent in the stabilization of the molecules by negative hyperconjugation, was analyzed through the transquinoidal mesomeric structures that result of π-conjugation in the Lewis and double bond–no–bond structure. An electron withdrawing substituent contributes to the stabilization of the axial isomers by the *endo*-anomeric effect and an electron donating group to the stabilization of the equatorial isomers by the *exo*-anomeric effect.

## 5. Experimental part

### 5.1. General

Melting points are uncorrected. The $^{1}H$, $^{13}C$, $^{31}P$, and $^{15}N$ NMR spectra were acquired on a JEOL Eclipse spectrometer at 400, 100.5, 161.8, and 40.5 MHz correspondingly, using $CDCl_3$ as solvent, at 27 °C, except in the case of the $^{15}N$ spectra of the ax-cis series, which were recorded in DMSO-$d_6$ at 75 °C in order to improve their solubility. Chemical shifts ($\delta$) are reported in ppm and coupling constants ($J$) in Hertz. The $^{31}P$ chemical shifts are reported in parts per million downfield (+) from 85% $H_3PO_4$ used as external standard. The $^{15}N$ spectra were measured with an INEPT pulse sequence and using $CH_3NO_2$ as reference. Mass spectra (EI) were measured on a Hewlett Packard 5989 A spectrometer using electron impact (EI) at 70 eV. The stereoisomeric mixture of 2,4-pentanodiol (*meso:d/l* in a 55:45 ratio) was obtained from the reduction of 2,4-pentanedione with sodium borohydride, as reported by Pritchard and Vollmer.[38] Compounds cis-ax **1**–**6** and cis-eq **1**–**6** were synthesized in oven-dried glassware under nitrogen atmosphere. Solvents and solutions were transferred by syringe-septum and cannula techniques. Solvents for the reactions, diethyl ether and toluene, were reagent grade and were dried and distilled from sodium/benzophenone immediately before use. Triethylamine was dried and distilled from $LiAlH_4$. Products were purified by flash column chromatography on silica gel 230–400 mesh, using a mixture of AcOEt/hexanes (1:9) as eluent. Yields are given for isolated products. Mixtures of AcOEt/hexanes or $CH_2Cl_2$/hexanes (1:3) were used for recrystallization. Crystallographic work was performed in an Enraf–Nonius Kappa CCD difractometer. Data collection Collect (Nonius BV, 1997–2000). Data reduction: Win GX,[39] solved by direct methods SHELXS97[40] and refined with SHELXL-97[41]: Molecular graphics: Diamond 2.1e (crystal impact 2003) and dihedral angles: Win GX.[39] Ab initio calculations were performed employing Gaussian 98.[15]

### 5.2. General procedure for the preparation of 2-p-X-anilino-2-thio-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphorinanes cis-ax (1–6) and cis-eq (1–6)

In a three-necked 2.0 L flask, fitted with dropping funnel, stir bar, and rubber septa, were placed 2.5 g (24 mmol) of 2,4-pentanodiol (mixture of stereoisomers) and 100 mL of dry diethyl ether. The solution was stirred at 0 °C and 2.1 mL (24 mmol) of phosphorus trichloride in 30.0 mL of diethyl ether were added slowly through the dropping funnel. The resulting solution was evaporated in a rotary evaporator and the concentrate transferred via cannula to a dropping funnel that contained 50 mL of dry toluene. The funnel was previously set in another 500 mL three-necked flask, equipped with stir bar and rubber septa, which contained 24 mmol of the corresponding *p*-X-substituted aniline and 3.4 mL (24 mmol) of triethylamine in 150 mL of dry toluene. The solution in the funnel was added dropwise, resulting in precipitation of a white solid (trietrylammonium chloride). The solid was filtered off through a filter tipped cannula and the filtrate added to a 500 mL flask, equipped with stir bar and reflux condenser, charged previously with 0.77 g (24 mmol) of elemental sulfur. The mixture was heated under reflux for 12 h. After cooling, the suspension was concentrated under vacuum. Purification of the crude product was accomplished by flash chromatography.

*5.2.1. ax-2-p-Methoxyanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**1**).* Mp 190–191 °C. Isolated yield (19.5%). $^{1}H$ NMR $\delta$ 1.42 (dd, 6H), 1.79 (dq, 1H), 1.92 (dt, 1H), 3.77 (s, 3H), 4.64 (m, 2H), 4.74 (d, $^{2}J_{HH}$=7.7, NH), 6.83 (d, $^{3}J_{HH}$=8.8, 2H), 7.01 (dd, $^{3}J_{HH}$=8.8, $^{4}J_{HP}$=0.5, 2H); $^{13}C$ NMR $\delta$ 22.4 (d, $C_{7,8}$), 40.5 (d, $C_5$) 55.6 (s, OMe), 76.0 (d, $C_{4,6}$); 114.8 (s, $C_{meta}$), 120.6 (d, $C_{ortho}$), 132.5 (s, $C_{ipso}$), 155.6 (s, $C_{para}$); $^{31}P$ NMR $\delta$ 60.60; $^{15}N$ NMR $\delta$ −298.64 (d). MS (*m*/*z*) 287 ($M^+$), 255 ($M^+$−32), 219 ($M^+$−68), 201 ($M^+$−86), 165 ($M^+$−122), 154 ($M^+$−133), 122 ($M^+$−165), 95 ($M^+$−192), 69 ($M^+$−218), 41 ($M^+$−246). Anal. Calcd for $C_{12}H_{18}O_3NPS$: C, 49.99%; H, 6.59%. Found: C, 50.20%; H, 6.50%.

*5.2.2. eq-2-p-Methoxyanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-eq-**1**).* Mp 101–102 °C. Isolated yield (8.5%). $^{1}H$ NMR $\delta$ 1.35 (dd, 6H), 1.58 (dt, 1H), 1.76 (dq, 1H), 3.78 (s, 3H), 4.84 (m, 2H), 5.24 (d, $^{2}J_{HH}$=14.7, NH), 6.81 (d, $^{3}J_{HH}$=8.9, 2H), 7.04 (dd, $^{3}J_{HH}$=8.9, $^{4}J_{HP}$=0.7, 2H); $^{13}C$ NMR $\delta$ 22.1 (d, $C_{7,8}$), 41.1 (d, $C_5$) 55.5 (s, OMe), 73.8 (d, $C_{4,6}$); 114.3 (s, $C_{meta}$), 122.6 (d, $C_{ortho}$), 131.4 (s, $C_{ipso}$), 156.2 (s, $C_{para}$); $^{31}P$ NMR $\delta$ 63.46; $^{15}N$ NMR $\delta$ −295.34 (d). MS (*m*/*z*) 287 ($M^+$), 254 ($M^+$−33), 219 ($M^+$−68), 201 ($M^+$−86), 170 ($M^+$−117), 154 ($M^+$−133), 95 ($M^+$−192), 69 ($M^+$−218), 41 ($M^+$−246). Anal. Calcd for $C_{12}H_{18}O_3NPS$. C, 49.99%; H, 6.59%. Found: C, 50.10%; H, 6.41%.

*5.2.3. ax-2-p-Cyclohexylanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**2**).* Mp 200 °C. Isolated yield (1.5%). $^{1}H$ NMR $\delta$ 1.23 (m, 1H), 1.34–1.48 (m, 4H), 1.41 (dd, 6H), 1.74 (m, 1H), 1.79 (dq, 1H), 1.79–1.96 (m, 4H), 1.92 (dt, 1H), 2.94 (tt, 1H), 4.65 (m, 2H), 4.83 (d, $^{2}J_{HP}$=6.8, NH), 6.97 (d, $^{3}J_{HH}$=8.5, 2H), 7.11 (d, $^{3}J_{HH}$=8.5, 2H); $^{13}C$ NMR $\delta$ 22.4 (d, $C_{7,8}$), 26.2 (s, $CH_2$), 26.9 (s, $CH_2$), 34.6 (s, $CH_2$), 40.5 (d, $C_5$), 43.8 (s, CH), 76.0 (d, $C_{4,6}$), 118.2 (d, $C_{ortho}$), 127.8 (s, $C_{meta}$), 137.0 (s, $C_{ipso}$), 142.3 (s, $C_{para}$); $^{31}P$ NMR $\delta$ 59.95; $^{15}N$ NMR $\delta$ −295.50 (d). MS (*m*/*z*): 339 ($M^+$), 271 ($M^+$−68), 228 ($M^+$−111), 130 ($M^+$−209), 92 ($M^+$−247), 69 ($M^+$−270), 41 ($M^+$−298). Anal. Calcd for $C_{17}H_{26}O_2NSP$: C, 60.15%; H, 7.72. Found: C, 60.20%; H, 8.02%.

*5.2.4. eq-2-p-Cyclohexylanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-eq-**2**).* Mp 145 °C. Isolated yield (50.2%). $^{1}H$ NMR $\delta$ 1.33–1.50 (m, 5H), 1.37 (dd, 6H), 1.69 (dt, 1H), 1.71–1.89 (m, 5H), 1.81 (dq, 1H), 2.44 (tt, 1H), 4.87 (m, 2H), 5.37 (d, $^{2}J_{HP}$=14.9, NH), 6.97 (d, $^{3}J_{HH}$=8.4, 2H), 7.09 (d, $^{3}J_{HH}$=8.4, 2H); $^{13}C$ NMR $\delta$ 22.2 (d, $C_{7,8}$), 26.2 (s, $CH_2$), 26.9 (s, $CH_2$), 34.6 (s, $CH_2$), 41.2 (d, $C_5$), 43.8 (s, CH), 74.0 (d, $C_{4,6}$), 119.3 (d, $C_{ortho}$), 127.5 (s, $C_{meta}$), 136.3 (s, $C_{ipso}$), 142.9 (s, $C_{para}$); $^{31}P$ NMR $\delta$ 63.02; $^{15}N$ NMR $\delta$ −291.38 (d). MS (*m*/*z*): 339 ($M^+$), 306 ($M^+$−33), 271 ($M^+$−68), 253 ($M^+$−86), 228 ($M^+$−111), 202 ($M^+$−137), 175 ($M^+$−164), 140 ($M^+$−199), 132 ($M^+$−207), 69 ($M^+$−270), 43 ($M^+$−296). Anal. Calcd for $C_{17}H_{26}O_2NSP$: C, 60.15%; H, 7.72. Found: C, 60.60%; H, 7.95%.

*5.2.5. ax-2-Anilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**3**).* Mp 204–205 °C. Isolated yield (15.0%). $^{1}H$ NMR $\delta$ 1.44 (dd, 6H), 1.81 (dq, 1H), 1.93 (dt, 1H), 4.65 (m, 2H), 4.88 (d, $^{2}J_{HP}$=7.5, NH), 7.02 (m, 1H), 7.05 (m, 2H), 7.28 (m, 2H) $^{13}C$ NMR $\delta$ 22.4 (d, $C_{7,8}$), 40.5 (d, $C_5$), 76.0 (d, $C_{4,6}$), 118.2 (d, $C_{ortho}$), 122.4 (s, $C_{para}$), 129.4 (s, $C_{meta}$), 139.6 (s, $C_{ipso}$); $^{31}P$ NMR $\delta$ 59.43; $^{15}N$ NMR $\delta$ −293.76 (d). MS (*m*/*z*) 257 ($M^+$), 225 ($M^+$−32), 216 ($M^+$−41), 189 ($M^+$−68), 155 ($M^+$−102), 124 ($M^+$−133), 97 ($M^+$−160), 93

($M^+-164$), 69 ($M^+-188$), 41 ($M^+-216$). Anal. Calcd for $C_{11}H_{16}O_2NPS$: C, 51.35%; H, 6.27%. Found: C, 51.17%; H, 6.58%.

*5.2.6. eq-2-Anilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphrinane (cis-eq-**3**).* Mp 114–115 °C. Isolated yield (37.5%). $^1$H NMR $\delta$ 1.38 (dd, 6H), 1.71 (dt, 1H), 1.82 (dq, 1H), 4.88 (m, 2H), 5.44 (d, $^2J_{HP}$=13.9 Hz, NH), 7.04 (m, 3H), 7.28 (m, 2H); $^{13}$C NMR $\delta$ 22.2 (d, $C_{7,8}$), 41.2 (d, $C_5$), 74.0 (d, $C_{4,6}$), 119.4 (d, $C_{ortho}$), 123.0 (s, $C_{para}$), 129.1 (s, $C_{meta}$), 138.7 (d, $C_{ipso}$); $^{31}$P NMR $\delta$ 62.94; $^{15}$N NMR $\delta$ −290.06 (d). MS (*m*/*z*) 257 ($M^+$), 224 ($M^+-33$), 215 ($M^+-42$), 189 ($M^+-68$), 160 ($M^+-97$), 140 ($M^+-117$), 94 ($M^+-163$), 93 ($M^+-164$), 69 ($M^+-188$), 41 ($M^+-216$). Anal. Calcd for $C_{11}H_{16}O_2NSP$: C, 51.35%; H, 6.27%. Found: C, 51.60%; H, 6.33%.

*5.2.7. ax-2-p-Chloroanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**4**).* Mp 245–246 °C. Isolated yield 18.9%. $^1$H NMR $\delta$ 1.43 (dd, 6H), 1.80 (dq, 1H), 1.92 (dt, 1H), 4.62 (m, 2H), 4.8 (d, $^2J_{HP}$=7.4, NH), 6.92 (d, $^3J_{HH}$=8.7, 2H), 7.17 (d, $^3J_{HH}$=8.7, 2H), $^{13}$C NMR $\delta$ 22.4 (d, $C_{7,8}$), 40.4 (d, $C_5$), 76.2 (d, $C_{4,6}$), 119.5 (d, $C_{ortho}$), 129.4 (s, $C_{meta}$), 138.1 (s, $C_{ipso}$); $^{31}$P NMR $\delta$ 59.43; $^{15}$N NMR $\delta$ −293.67 (d). MS (*m*/*z*) 291 ($M^+$), 223 ($M^+-68$), 205 ($M^+-86$), 170 ($M^+-121$), 158 ($M^+-133$), 127 ($M^+-164$), 99 ($M^+-192$), 69 ($M^+-222$), 41 ($M^+-250$). Anal. Calcd for $C_{11}H_{15}O_2NSPCl$: C, 45.29%; H, 5.18. Found: C, 45.42%; H, 5.26%.

*5.2.8. eq-2-p-Chloroanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-eq-**4**).* Mp 97–99 °C. Isolated yield 6.7%. $^1$H NMR $\delta$ 1.37 (dd, 6H), 1.67 (dt, 1H), 1.82 (dq, 1H), 4.87 (m, 2H), 5.44 (d, $^2J_{HP}$=13.4, NH), 7.0 (d, $^3J_{HH}$=8.8, 2H), 7.23 (d, $^3J_{HH}$=8.8, 2H); $^{13}$C NMR $\delta$ 22.1 (d, $C_{7,8}$), 41.1 (d, $C_5$), 74.1 (d, $C_{4,6}$), 121.0 (d, $C_{ortho}$), 128.2 (s, $C_{para}$), 129.0 (s, $C_{meta}$), 137.5 (d, $C_{ipso}$); $^{31}$P NMR $\delta$ 62.87; $^{15}$N NMR $\delta$ −290.88 (d). MS (*m*/*z*) 291 ($M^+$), 223 ($M^+-68$), 205 ($M^+-86$), 170 ($M^+-121$), 158 ($M^+-133$), 127 ($M^+-164$), 99 ($M^+-192$), 69 ($M^+-222$), 41 ($M^+-250$) Anal. Calcd for $C_{11}H_{15}O_2NSPCl$: C, 45.29%; H, 5.18. Found: C, 44.96%; H, 6.61%.

*5.2.9. ax-2-p-Cyanoanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**5**).* Mp 113–116 °C. Isolated yield (22.4%). $^1$H NMR $\delta$ 1.39 (dd, 6H), 1.81 (dq, 1H), 1.90 (dt, 1H), 4.62 (m, 2H), 5.85 (d, NH), 7.14 (d, $^3J_{HH}$=8.4, 2H), 7.54 (d, $^3J_{HH}$=8.4, 2H); $^{13}$C NMR $\delta$ 22.3 (d, $C_{7,8}$), 40.4 (d, $C_5$), 75.6 (d, $C_{4,6}$), 105.6 (s, $C_{para}$), 118.0 (d, $C_{ortho}$), 118.9 (s, CN), 133.5 (s, $C_{meta}$), 144.3 (s, $C_{ipso}$); $^{31}$P NMR $\delta$ 57.35; $^{15}$N NMR $\delta$ −285.80 (d). MS (*m*/*z*) 282 ($M^+$), 255 ($M^+-27$), 241 ($M^+-41$), 214 ($M^+-68$), 179 ($M^+-103$), 149 ($M^+-133$), 149 ($M^+-133$), 118 ($M^+-164$), 90 ($M^+-192$), 69 ($M^+-213$), 41 ($M^+-241$). Anal. Calcd for $C_{12}H_{16}O_2N_2SP$: C, 51.06%; H, 5.36% N, 9.92%. Found: C, 50.53%; H, 5.31%, N, 9.90%.

*5.2.10. eq-2-p-Cyanoanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-eq-**5**).* Mp 174–175 °C. Isolated yield (1.5%). $^1$H NMR $\delta$ 1.36 (dd, 6H), 1.75 (dt, 1H), 1.87 (dq, 1H), 4.89 (m, 2H), 6.29 (d, $^2J_{HP}$=13.4, NH), 7.12 (d, $^3J_{HH}$=8.6, 2H), 7.52 (d, $^3J_{HH}$=8.6, 2H); $^{13}$C NMR $\delta$ 22.5 (d, $C_{7,8}$), 41.6 (d, $C_5$), 74.9 (d, $C_{4,6}$), 105.6 (s, $C_{para}$), 119.1 (d, $C_{ortho}$), 119.4 (s, CN), 133.8 (s, $C_{meta}$), 143.6 (d, $C_{ipso}$); $^{31}$P NMR $\delta$ 62.25; $^{15}$N NMR $\delta$ −284.46 (d). MS (*m*/*z*) 282 ($M^+$), 249 ($M^+-33$), 214 ($M^+-68$), 196 ($M^+-86$), 165 ($M^+-117$), 149 ($M^+-133$), 118 ($M^+-164$), 85 ($M^+-197$), 69 ($M^+-213$), 41 ($M^+-241$). Anal. Calcd for $C_{12}H_{15}O_2NSP$: C, 51.06%; H, 5.35%. Found: C, 51.01%; H, 5.06%

*5.2.11. ax-2-p-Nitroanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-ax-**6**).* Mp 226–229 °C. Isolated yield (6.5%). $^1$H NMR $\delta$ 1.43 (dd, 6H), 1.83 (dt, 1H), 1.93 (dq, 1H), 4.63 (m, 2H), 4.89 (m, NH), 7.14 (d, $^3J_{HH}$=9.1, 2H), 8.17 (d, $^3J_{HH}$=8.16, 2H); $^{13}$C NMR $\delta$ 22.2 (d, $C_{7,8}$), 40.4 (d, $C_5$), 76.8 (d, $C_{4,6}$), 117.3 (d, $C_{ortho}$), 125.6 (s, $C_{meta}$), 142.4 (s, $C_{para}$), 146.0 (s, $C_{ipso}$); $^{31}$P NMR $\delta$ 57.24; $^{15}$N NMR $\delta$ −283.79 (d). MS (*m*/*z*) 302 ($M^+$), 272 ($M^+-30$), 236 ($M^+-66$), 234 ($M^+-68$), 187 ($M^+-115$), 170 ($M^+-132$), 138 ($M^+-164$), 69 ($M^+-233$), 41 ($M^+-261$). Anal. Calcd for $C_{11}H_{15}O_4N_2SP$: C, 43.70%; H, 5.00%. Found: C, 43.59%; H, 5.16%.

*5.2.12. eq-2-p-Nitroanilino-2-thio-cis-4,6-dimethyl-1,3,2λ$^5$-dioxaphosphinane (cis-eq-**6**).* Mp 133–136 °C. Isolated yield (13.6%). $^1$H NMR $\delta$ 1.41 (dd, 6H), 1.78 (dt, 1H), 1.91 (dq, 1H), 4.89 (m, 2H), 6.04 (d, $^2J_{HP}$=13.0, NH), 7.13 (d, $^3J_{HH}$=9.1, 2H), 8.17 (d, $^3J_{HH}$=8.16, 2H); $^{13}$C NMR $\delta$ 22.3 (d, C7,8), 41.3 (d,C5), 74.5 (d, $C_{4,6}$), 118.2 (d, $C_{ortho}$), 125.3 (s, $C_{meta}$), 142.8 (s, $C_{para}$), 144.9 (d, $C_{ipso}$); $^{31}$P NMR $\delta$ 61.92; $^{15}$N NMR $\delta$ −283.60 (d). MS (*m*/*z*) 302 ($M^+$), 269 ($M^+-33$), 234 ($M^+-68$), 216 ($M^+-86$), 185 ($M^+-117$), 138 ($M^+-164$), 108 ($M^+-194$), 69 ($M^+-233$), 41 ($M^+-261$). Anal. Calcd for $C_{11}H_{15}O_4N_2SP$: C, 43.70%; H, 5.00%. Found: C, 43.92%; H, 5.02%.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.034.

## References and notes


1. (a) Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, NY, 1994, Chapter 11; (b) Kellie, G. M.; Ridell, F. G. *Top. Stereochem.* **1974**, *8*, 225.
2. (a) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444; (b) Ridell, F. G.; Robinson, J. T. *Tetrahedron* **1967**, *23*, 3417; (c) Pihlaja, K. *Acta Chem. Scand.* **1948**, *22*, 716.
3. Excellent reviews about this topic can be found in: (a) Bentrude, W. G. In *Steric and Stereoelectronic Effects in 1,3,2-Dioxaphosphorinanes in Conformational Behavior of Six-Membered Rings: Analysis, Dynamics and Stereoelectronic Effects*; Juaristi, E., Ed.; VCH: New York, NY, 1995; (b) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187; (c) Gorenstein, D. G. *Chem. Rev.* **1987**, *87*, 1049.
4. (a) Ref. 3a, and 3b and references cited there. (b) Bentrude, W. G.; Tan, H.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4666; (c) Van Nuffel, P.; Van Alsenoy, C.; Lenstra, A. T. H.; Geise, H. J. *J. Mol. Struct.* **1984**, *125*, 1.
5. (a) Majoral, J. P.; Bergounhou, C.; Navech, J. *Bull Soc. Chim. Fr.* **1973**, 3146; (b) Brault, J.-F.; Majoral, J. P.; Savignac, P.; Navech, J. *Bull Soc. Chim. Fr.* **1973**, 3149.
6. (a) Stewart, E. L.; Nevins, N.; Allinger, N. L.; Bowen, J. P. *J. Org. Chem.* **1999**, *64*, 5350; (b) Arshinova, R. P. *Russ. Chem. Rev.* **1984**, *53*, 351; (c) Cramer, C. J. *J. Mol. Struct. (THEOCHEM)* **1996**, *370*, 135.
7. For a further discussion on orbital hyperconjugation see: (a) Thatcher, G. R. J. *The Anomeric Effect and Associated Stereoelectronic Effects*; American Chemical Society: Washington, DC, 1992; Vol. 539; (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019; (c) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer: Heidelberg, Germany, 1983.
8. Ref. 3a pp 277–278. (b) Verkade, J. G. *Phosphorus Sulfur* **1976**, *2*, 251.
9. Muiphy, P. C.; Tebby, J. C. dπ–pπ Bonding Effects on 31P NMR Chemical Shift of *N*-Aryliminophosphoranes In *Phosphorus Chemistry, Proceedings of the 1981 International Conference*; Quin, L. D., Verkade, J. G., Eds.; ACS Symposium Series; ACS: Washington, D.C., 1981; Vol. 171, p 573.
10. Gilheany, D. G. *Chem Rev.* **1994**, *94*, 1339.
11. Dobado, J. A.; Martínez-García, H.; Molina-Molina, J.; Sundberg, M. R. *J. Am. Chem. Soc.* **1998**, *120*, 8461.
12. Stec, W. J.; Okrusek, A. *J. Chem. Soc. Perkin 1* **1975**, 1828.
13. Bentrude, W.; Setzer, W. N.; Newton, M.; Meehan, E. J.; Ramli, E.; Khan, M.; Ealick, S. *Phosphorus, Sulfur Silicon* **1991**, *57*, 25.
14. (a) Domínguez, Z. J.; Cortez, M. T.; Gordillo, B. *Tetrahedron* **2001**, *57*, 9799; (b) Hommer, H.; Domínguez, Z.; Gordillo, B. *Acta Crystallogr.* **1998**, *C54*, 832.
15. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Stain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, A. M.; Peng, A. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnsons, B.; Chen, W.; Wong, M. W.; Andress, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian,: Pittsburgh PA, 1998.
16. The cis/ *trans* diastereoselectivity observed for the phosphochloridites I, is due to the selective decomposition of the *trans*- ax isomer by traces of humidity and the hydrochloric acid evolved during the reaction [see discussion in Gordillo, B.; Hernández, J. *Org. Prep. Proc. Intern. (OPPI)* **1997**, *29*, 195 Based on the amount of the *meso* diol, the diastereomer I (cis- ax) is obtained in ~ 85% yield, when isolated.
17. (a) Stewart, E. L.; Nevins, N.; Allinger, N. L.; Bowen, J. P. *J. Org. Chem.* **1997**, *62*, 5198; (b) Leyssens, T.; Peeters, D. *J. Org. Chem.* **2008**, *73*, 2725.
18. Ref. 1, p. 716.

19. Although we observed that thiophosphoramidates have almost $sp^2$-hybridized oxygens, the $sp^3$ hybridization for oxygens in P (IV) containing compounds has also been considered in theoretical studies (Ref. 6a). See also the comment on Ref. 36 of this work.
20. Nifantiev, E. E.; Sorokina, S. F.; Borisenko, A. A. *J. Gen. Chem.* **1984**, *55*, 1481.
21. Hernández, J.; Ramos, R.; Sastre, N.; Meza, R.; Hommer, H.; Salas, M.; Gordillo, B. *Tetrahedron* **2004**, *60*, 10927.
22. Jameson, C. J.; Mason, J. In *Multinuclear NMR*; Mason, J., Ed.; Plenum: New York, NY, 1987.
23. Modro, A. M.; Modro, T. A.; Bernatowicz, P.; Schilf, W.; Stefaniak, L. *Magn. Reson. Chem.* **1997**, *35*, 774.
24. Gray, G. A.; Buchanan, G. W.; Morin, F. G. *J. Org. Chem.* **1979**, *44*, 1768.
25. Hansch, C.; Leo, A.; Taft, R. W. *Chem. Rev.* **1991**, *91*, 165.
26. Kuivalainen, T.; El-Bahraoui, J.; Uggula, R.; Kostiainen, R.; Sundberg, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 8073.
27. (a) Gorenstein, D. G. *J. Am. Chem. Soc.* **1975**, *97*, 898; (b) Gorenstein, D. G. *J. Am. Chem. Soc.* **1977**, *99*, 2254.
28. Huheey, J.E.; Keiter, E.A.; Keiter, R.L. Inorganic Chemistry. Priciples of Structure and Reactivity. Harper Collins Collegue: New York, NY, 1993, 4th ed.
29. Salas, M.; Gordillo, B.; González, F. J. *Arkivoc* **2003**, *Xi*, 72; http://www.arkat-usa.org/get-file/19823/.
30. (a) Stec, W. J. *Acc. Chem. Res.* **1983**, *16*, 411; (b) Tomasz, J.; Bottka, S.; Radics, L. *NucleosidesNucleotides* **1989**, *8*, 1297.
31. As stated by Eliel et al. (Ref. 1 p. 687), there exist a compromise between torsional angles and valency angles in which the total strain of the molecule is minimized. The mathematical cosine equations relating torsional angles and bond angles in cyclohexane and heterocyclic compounds are proposed in Romers, C.; Altona, H. R.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 39.
32. Ref. 1 p. 770.
33. (a) Bentrude, W. G.; Setzer, W. N.; Ramli, E.; Khan, M.; Sopchik, A. E. *J. Org. Chem.* **1991**, *56*, 6127; (b) Cameron, T. S.; Galdecki, Z.; Karolak-Wojciechowska, J. *Acta Crystallogr., Sect. B* **1976**, *B32*, 492.
34. Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, NY, 1983.
35. Perrin, C. L.; Kuperman, J. *J. Am. Chem. Soc.* **2003**, *125*, 8846.
36. Considering that the non-boding electron pairs on oxygen participate in the anomeric effect; the discussion on their canonical or $sp^3$ nature, become important (see Ref 7c, p. 39). In the studied dioxaphosphinanes, the hybridization on the oxygens is closer to $sp^2$ (COP angles $\sim 118^\circ$) than the hybridization of the oxygens of 1,3-dioxanes (COC angles $\sim 115^\circ$) where the anomeric effect is also present Uehara, F.; Sato, M.; Kaneko, C.; Kurihara, H. *J. Org. Chem.* **1999**, *64*, 1436.
37. Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102.
38. Pritchard, G. J.; Vollmer, R. J. *J. Org. Chem.* **1963**, *28*, 1545.
39. Farrugia, L. J. *J. Appl. Crystallogr.* **1999**, *32*, 837.
40. Sheldrick, G. M. *SHELEX97: Program for the solution of Crystal Structures*; University of Göttingen: Germany, 1997.
41. Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112.