The lack of influence of electronic effects on the stereochemistry of the oxidation of aryl thiophosphates

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A series of epimeric six-membered cyclic aryl thiophosphates **1**–**7** were oxidized to their corresponding phosphates by means of a mixture of aqueous hydrogen peroxide (30%) and hydrogen chloride. The oxidation, under these conditions, is highly stereospecific so that the products were obtained in quantitative yields with retention of configuration at the phosphorus center. Our results do not support the participation of pentacoordinate species as plausible intermediates of the oxidation reaction.

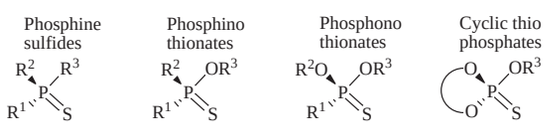
Organophosphorus compounds play a ubiquitous role in metabolic oxidation processes.[1,2] The widespread biological activity of phosphate derivatives, as thiophosphates,[3] which are active not only as insecticides[4] but also as antiviral drugs,[5] has prompted their investigation, particularly in relation to the stereochemistry and mechanism of their oxidation.

Dramatic variations of the stereochemical outcome of the oxidation of thiophosphoryl compounds were reported earlier.[6] As a consequence, several research laboratories became involved in the problem, and very interesting results were derived from these studies.[7–16] A brief summary of the findings is as follows. The stereochemistry of the oxidation process depends mainly on the nature of the oxidizing agent, on the structures of the thio derivatives, on pH, on solvent; and least, on temperature and reaction times. A list of oxidizing agents and the stereochemistry with which the oxidation of several thiophosphoryl compounds was carried out are summarized in Table 1.

As observed, phosphine sulfides react with conventional neutral or acidic oxidizing agents with overall inversion of configuration, whereas cyclic thiophosphates are converted into their corresponding oxo derivatives with net retention of configuration. More striking is the behavior of phosphino and phosphono thionates, which are oxidized with either inversion or retention of configuration even though the same type of oxidizing agents are used, *i.e.* peroxy acids.[6] A rationale of the results for the oxidation of thiophosphoryl compounds by hydrogen peroxide has been provided by Stec and Michalski[13] who postulated that the first step in the reaction was the nucleophilic attack of sulfur on hydrogen peroxide with the concomitant formation of a thiophosphonium intermediate. The second step was then the formation of a pentacoordinate intermediate which determined the stereochemical course of the reaction. An *in line* arrangement of the attacking–departure groups in the *apical* positions of the pentacovalent intermediate produces the oxo product with inversion of configuration, and an *apical–equatorial* arrangement leads to the product with retention of configuration due to the participation of pseudorotation (Scheme 1).

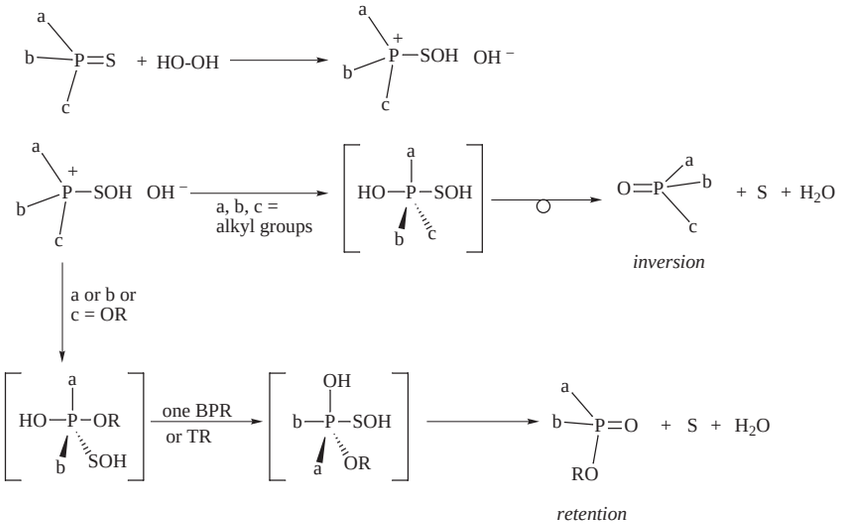
It is pertinent to emphasize that in several reactions of organophosphorus compounds in which pentacovalent species are postulated as intermediates, for example the alkaline hydrolysis of phosphates,[17] it has been found that the participation of pseudorotation depends highly on the electronic characteristics of the phosphorus atom. For aryloxy phosphorus containing heterocycles, the electronic environment at phosphorus can be modified by the presence of electron releasing or electron withdrawing groups in the aromatic residue. Therefore, as an additional proof of the participation of pentacoordinate intermediates in the oxidation of thiophosphoryl compounds, we planned to study the stereochemical course of the oxidation of the epimeric thiophosphates **1**–**7** (Scheme 2) with hydrogen peroxide in acidic media. If participation of pentacoordinate intermediates occurs a mixture of retention and inversion products which varies with the electronic characteristics of the aryloxy group may be anticipated (see below). The results of these studies are discussed herein.

Table 1 Stereoselectivity in the oxidation of thiophosphoryl compounds



R^1, R^2, or R^3 = alkyl substituents

Oxidizing agent	Thio derivative	Overall stereoselectivity	Reference
$KMnO_4$–py	I	Retention	7
HNO_3	I	Inversion	8
HNO_3	III	Inversion	8
HNO_3	IV	Retention	9
N_2O_4–CF_3CO_2H	I	Inversion	8
N_2O_4	III	Retention	9
MCPBA	II	Retention	6
MCPBA–CF_3CO_2H	II	Inversion	6*a*
O_3	III	Retention	10
O_3	IV	Retention	10
DMSO–H_2SO_4	I	Inversion	11*a*
DMSO–H_2SO_4	IV	Retention	11*b*
DMSO–HNO_3	I	Inversion	11*c*
DMSO–I_2	I	Inversion	11*d*
DMSO–I_2	IV (R^3 = H)	Inversion	11*e*
TFAA	I	Racemization	12
H_2O_2	I	Inversion	13
H_2O_2–CF_3CO_2H	I	Inversion	13
H_2O_2	IV	Retention	13
Me_2Se=O	I	Inversion	14
Me_2Se=O	IV	Retention	14
Cl_3CCHO	IV	Retention	15



Scheme 1 [6]

trans *cis*

	σ_p [a]
1, Ar = *p*-MeO-C_6H_4-	–0.27
2, Ar = *p*-Me-C_6H_4-	–0.17
3, Ar = *p*-Ph-C_6H_4-	–0.01
4, Ar = C_6H_5-	0
5, Ar = *p*-Br-C_6H_4-	0.23
6, Ar = *p*-CN-C_6H_4-	0.66
7, Ar = *p*-NO_2-C_6H_4-	0.78

[a] Values in ref. 18.

Scheme 2

Experimental

Melting points were obtained in a Mel-Temp II apparatus with an open capillary tube. Microanalyses were performed by Galbraith Laboratories, Inc. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solutions on a Jeol GSX-270 spectrometer (at 270 and 67.5 MHz, respectively) and on a Jeol Eclipse 400 (at 399.8 and 100.5 MHz respectively). Chemical shifts (δ) are referenced to internal $(CH_3)_4Si$. ^{31}P NMR spectra were recorded, in $CDCl_3$, at 109.25 MHz on the Jeol GSX-270 spectrometer and at 161.83 MHz on the Jeol Eclipse 400 spectrometer. Chemical shifts are reported in ppm downfield (+) from external 85% H_3PO_4. The mass spectrometry analyses were obtained on a Hewlett Packard 5989A spectrometer.

cis- and *trans*-Aryl thiophosphates (1–7)

These compounds were prepared from *meso*-pentane-2,4-diol [19] by the stereospecific approach described in ref. 20.

General procedure for the oxidation of *cis*- or *trans*-aryl thiophosphates (1–7)

In a 100 mL round-bottomed flask, equipped with a magnetic stirrer, were placed 0.1 g of the aryl thiophosphate and 5 mL of 1,4-dioxane. The mixture was stirred until the thiophosphate was totally dissolved, and then 100 equiv. of hydrogen peroxide (30% aqueous solution) followed by 8 equiv. of hydrogen chloride (37% aqueous solution) were added. The reaction mixture was stirred for an additional 12 h at ambient temperature and then a solution of saturated sodium bicarbonate was added until pH = 7 was reached. The organic layer was extracted with 20 mL of dichloromethane, dried over anhydrous sodium sulfate, filtered, and concentrated in a rotary evaporator. Most of the solid phosphates were purified by recrystallization; liquids were purified by flash column chromatography using a 50% hexanes–ethyl acetate solution as eluent.

Stereochemistry of the oxidation reactions

Thiophosphates (**1**–**7**) were reacted with hydrogen peroxide in hydrogen chloride following the procedure described above. Crude materials were analyzed by ^{31}P NMR spectroscopy of an aliquot of the reaction solution. Complete disappearance of the starting material was observed [^{31}P NMR: $\delta_{(trans)}$ = 54.3 to 56.2 ppm; $\delta_{(cis)}$ = 59.2 to 61.0 ppm]. Only one oxo product was formed [^{31}P NMR: $\delta_{(trans)}$ = −12.2 to −15 ppm; $\delta_{(cis)}$ = −9.7 to −12.2 ppm]. The stereochemistry of the products was assigned for the isolated materials, according to the NMR properties of phosphates reported in refs. 17, 21 and 22. See Tables 2 and 3.

Oxidations-in-competition experiments

A solution of 0.01 g of aryl thiophosphate (**1**, **4** or **7**) in 0.22 mL of 1,4-dioxane was added to an NMR tube. A 30% aqueous solution of hydrogen peroxide (50 equiv.) was then added followed by 8 equiv. of hydrogen chloride (37% aqueous solution). The NMR tube was capped and introduced into the NMR equipment immediately. The reaction was followed by ^{31}P NMR until no starting material was observed. The spectra were registered in accord with the times reported in Table 4. Only one oxo product was detected (see chemical shifts in Tables 2 and 3). The area ratio of the thiophosphate/phosphate was calculated electronically.

r-2-(*p*-Methoxyphenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-8)†

Purification by flash column chromatography gave 0.090 g (95.7%) of a solid, mp 75–77 °C. The NMR spectral data for this compound are in agreement with those reported in the literature.[17,21]

r-2-(*p*-Methoxyphenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-8)

Purification by flash column chromatography resulted in 0.088 g (93.6%) of a yellow oil. The NMR spectral data for this compound are in accordance with those reported in the literature.[17,21]

† Phosphinanes were previously called phosphorinanes (the change is in accord with recommendation RB-1.1 Hantsch–Widman System, IUPAC, 1993).

r-2-(*p*-Methylphenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-9)

Recrystallization from ethyl acetate afforded 0.064 g (68.1%) of colorless crystals, mp 85–87 °C. ^{1}H NMR: δ 1.40 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.75 (dt, J_{gem} = 13.9 Hz, J_{anti} = 9.6 Hz, 1 H, H_5 *ax*.), 1.85 (~dq, J_{gem} = 13.9 Hz, J_{gauche} = 2.7 Hz, J_{HCCOP} = 2.2 Hz, 1 H, H_5 *eq*.), 2.31 (s, 3 H), 4.70 (m, 2 H, $H_{4,6}$), 7.12 (br s, 4 H, $H_{arom.}$); ^{13}C NMR: δ 20.70 (s, 1 C), 22.07 (d, 2 C), 40.45 (d, 1 C), 76.45 (d, 2 C), 119.15 (d, 2 C), 130.24 (s, 2 C), 134.41 (s, 1 C), 148.37 (d, 1 C); MS: *m*/*z* 256 (M^+), 215 ($M^+ - 41$), 188 ($M^+ - 68$), 108 ($M^+ - 148$), 90 ($M^+ - 166$), 69 ($M^+ - 187$), 41 ($M^+ - 215$). Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.23; H, 6.69. Found: C, 56.28; H, 6.86%.

r-2-(*p*-Methylphenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-9)

Recrystallization from ethyl acetate gave 0.071 g (75.5%) of colorless crystals, mp 79–81 °C. ^{1}H NMR: δ 1.36 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.66 (dt, J_{gem} = 14.6 Hz, J_{anti} = 9.6 Hz, 1 H, H_5 *ax*.), 1.83 (~dq, J_{gem} = 14.6 Hz, J_{gauche} = 4.0 Hz, J_{HCCOP} = 2.2 Hz, 1 H, H_5 *eq*.), 2.32 (s, 3 H), 4.77 (m, 2 H, $H_{4,6}$), 7.12 (br s, 4 H, $H_{arom.}$); ^{13}C NMR: δ 20.76 (s, 1 C), 22.21 (d, 2 C), 40.28 (d, 1 C), 75.87 (d, 2 C), 120.06 (d, 2 C), 130.02 (s, 2 C), 134.74 (s, 1 C), 148.56 (d, 1 C); MS: *m*/*z* 256 (M^+), 215 ($M^+ - 41$), 188 ($M^+ - 68$), 108 ($M^+ - 148$), 90 ($M^+ - 166$), 69 ($M^+ - 187$), 41 ($M^+ - 215$). Anal. Calcd for $C_{12}H_{17}O_4P$: C, 56.23; H, 6.69. Found: C, 56.08; H, 6.99%.

r-2-(*p*-Phenylphenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-10)

Recrystallization from ethyl acetate gave 0.072 g (75.8%) of colorless crystals, mp 145–146 °C. ^{1}H NMR: δ 1.39 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.74 (dt, J_{gem} = 14.6 Hz, J_{anti} = 9.5 Hz, 1 H, H_5 *ax*.), 1.85 (dq, J_{gem} = 14.6 Hz, J_{gauche} = 2.2 Hz, J_{HCCOP} = 2.2 Hz, 1 H, H_5 *eq*.), 4.70 (m, 2 H, $H_{4,6}$), 7.31 (~d, J_{HCCH} = 7.3 Hz, 2 H, $H_{arom.}$), 7.31 (~t, J_{HCCH} = 7.3 Hz, 1 H, $H_{arom.}$), 7.45 (t, J_{HCCH} = 7.5 Hz, 2H, $H_{arom.}$), 7.56 (m, 4H, $H_{arom.}$); ^{13}C NMR: δ 21.93 (d, 2 C), 40.31 (d, 1 C), 76.60 (d, 2 C), 119.66 (d, 2 C), 126.85 (s, 2 C), 127.19 (s, 1 C), 128.37 (s, 2 C), 128.70 (s, 2 C), 137.9 (s, 1 C), 140.05 (s, 1 C), 149.96 (d, 1 C); MS: *m*/*z* 318 (M^+), 276 ($M^+ - 42$), 250 ($M^+ - 68$), 232 ($M^+ - 86$), 170 ($M^+ - 148$), 141 ($M^+ - 177$), 41 ($M^+ - 277$). Anal. Calcd for $C_{17}H_{19}O_4P$: C, 64.13; H, 6.02. Found: C, 63.54; H, 5.70%.

r-2-(*p*-Phenylphenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-10)

Purification by flash column chromatography gave 0.070 g (73.7%) of a solid which was recrystallized from a mixture of 80% hexanes–methylene chloride to afford colorless crystals, mp 93–95 °C. ^{1}H NMR: δ 1.33 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.2 Hz, 6 H, CH_3's at C_4 and C_6), 1.66 (dt, J_{gem} = 14.6 Hz, J_{anti} = 10.9 Hz, 1 H, H_5 *ax*.), 1.80 (~dq, J_{gem} = 14.6 Hz, J_{gauche} = 2.5 Hz, J_{HCCOP} = 2.2 Hz, 1 H, H_5 *eq*.), 4.75 (m, J_{HCOP} = 2.5 Hz, 2 H, $H_{4,6}$), 7.29 (dd, J_{HCCH} = 8.0 Hz, J_{HCCOP} = 1.1 Hz, J_{HCCH} = 7.3 Hz, 3 H, $H_{arom.}$), 7.34 (t, J_{HCCH} = 7.3 Hz, 2 H, $H_{arom.}$), 7.55 (d, 4H, $H_{arom.}$); ^{13}C NMR: δ 22.06 (d, 2 C), 40.22 (d, 1 C), 76.06 (d, 2 C), 120.56 (d, 2 C), 126.97 (s, 2 C), 127.26 (s, 1 C), 128.24 (s, 2 C), 128.77 (s, 2 C), 138.24 (s, 1 C), 140.17 (s, 1 C), 150.15 (d, 1 C); MS: *m*/*z* 318 (M^+), 276 ($M^+ - 42$), 250 ($M^+ - 68$), 232 ($M^+ - 86$), 170 ($M^+ - 148$), 141 ($M^+ - 177$), 41 ($M^+ - 277$). Anal. Calcd for $C_{17}H_{19}O_4P$: C, 64.13; H, 6.02. Found: C, 64.03; H, 6.25%.

r-2-(Phenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-11)

Purification by flash column chromatography gave 0.037 g (39.4%) of a solid, mp 88–90 °C. The NMR spectral data for this compound are in agreement with those reported in the literature.[21,22]

r-2-(Phenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-11)

Purification by flash column chromatography resulted in 0.040 g (42.6%) of a yellow oil. The NMR spectral data for this compound are in accordance with those reported in the literature.[21,22]

r-2-(*p*-Bromophenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-12)

Recrystallization from ethyl acetate gave 0.090 g (94.7%) of colorless crystals, mp 137–139 °C. ^{1}H NMR: δ 1.40 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.78 (dt, J_{gem} = 14.6 Hz, J_{anti} = 9.3 Hz, 1 H, H_5 *ax*.), 1.86 (~dq, J_{gem} = 14.6 Hz, J_{gauche} = 4.1 Hz, J_{HCCOP} = 2.5 Hz, 1 H, H_5 *eq*.), 4.67 (m, 2 H, $H_{4,6}$), 7.16 (~d, J_{HCCH} = 8.8 Hz, 2 H, $H_{arom.}$), 8.43 (d, 2H, $H_{arom.}$); ^{13}C NMR: δ 23.16 (d, 2 C), 41.5 (d, 1 C), 78.07 (d, 2 C), 118.86 (s, 1 C), 122.48 (d, 2 C), 133.85 (s, 2 C), 150.86 (d, 1 C); MS: *m*/*z* 320 (M^+), 281 ($M^+ - 39$), 253 ($M^+ - 67$), 234 ($M^+ - 86$), 172 ($M^+ - 148$), 68 ($M^+ - 252$), 41 ($M^+ - 279$). Anal. Calcd for $C_{11}H_{14}O_4PBr$: C, 41.25; H, 4.41. Found: C, 41.02; H, 4.54%.

r-2-(*p*-Bromophenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-12)

Recrystallization from ethyl acetate afforded 0.080 g (73%) of colorless crystals, mp 49–51 °C. ^{1}H NMR: δ 1.30 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.6 Hz, 6 H, CH_3's at C_4 and C_6), 1.61 (dt, J_{gem} = 14.6 Hz, J_{anti} = 9.9 Hz, 1 H, H_5 *ax*.), 1.80 (dq, J_{gem} = 14.6 Hz, J_{gauche} = 2.6 Hz, J_{HCCOP} = 2.6 Hz, 1 H, H_5 *eq*.), 4.73 (m, J_{HCOP} = 2.6 Hz, 2 H, $H_{4,6}$), 7.05 (dd, J_{HCCH} = 8.6 Hz, J_{HCCOP} = 1.3 Hz, 2 H, $H_{arom.}$), 7.38 (d, 2 H, $H_{arom.}$); ^{13}C NMR: δ 21.17 (d, 2 C), 39.19 (d, 1 C), 75.21 (d, 2 C), 117.14 (s, 1 C), 121.14 (d, 2 C), 131.28 (s, 2 C), 148.79 (d, 1 C); MS: *m*/*z* 320 (M^+), 281 ($M^+ - 39$), 253 ($M^+ - 67$), 234 ($M^+ - 86$), 172 ($M^+ - 148$), 68 ($M^+ - 252$), 41 ($M^+ - 279$). Anal. Calcd for $C_{11}H_{14}O_4PBr$: C, 41.25; H, 4.41. Found: C, 41.34; H, 4.60%.

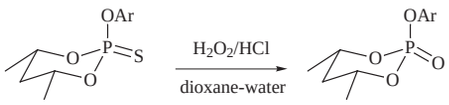
r-2-(*p*-Cyanophenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-13)

Recrystallization from a mixture of 90% hexanes–methylene chloride gave 0.040 g (42.6%) of colorless crystals, mp 87–89 °C. ^{1}H NMR: δ 1.42 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.82 (dt, J_{gem} = 14.6 Hz, J_{anti} = 10.9 Hz, 1 H, H_5 *ax*.), 1.89 (dq, J_{gem} = 14.6 Hz, J_{gauche} = 2.5 Hz, J_{HCCOP} = 2.5 Hz, 1 H, H_5 *eq*.), 4.79 (m, 2 H, $H_{4,6}$), 7.36 (~d, J_{HCCH} = 8.4 Hz, 2 H, $H_{arom.}$), 8.43 (d, 2H, $H_{arom.}$); ^{13}C NMR: δ 22.05 (d, 2 C), 40.3 (d, 1 C), 77.3 (d, 2 C), 108.75 (s, 1 C), 118.19 (s, 1 C), 120.51 (d, 2 C), 134.23 (s, 2 C), 153.94 (d, 1 C); MS: *m*/*z* 267 (M^+), 226 ($M^+ - 41$), 200 ($M^+ - 67$), 181 ($M^+ - 86$), 119 ($M^+ - 148$), 68 ($M^+ - 199$), 41 ($M^+ - 226$). Anal. Calcd for $C_{12}H_{14}O_4PN$: C, 53.92; H, 5.28. Found: C, 54.01; H, 5.43%.

r-2-(*p*-Cyanophenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-13)

Recrystallization from ethyl acetate afforded 0.043 g (45.7%) of colorless crystals, mp 75–76 °C. ^{1}H NMR: δ 1.40 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 2.5 Hz, 6 H, CH_3's at C_4 and C_6), 1.77 (dt, J_{gem} = 14.6 Hz, J_{anti} = 11.3 Hz, 1 H, H_5 *ax*.), 1.93 (~dq, J_{gem} = 14.6 Hz, J_{gauche} = 2.9 Hz, J_{HCCOP} = 2.5 Hz, 1 H, H_5 *eq*.), 4.81 (m, J_{HCOP} = 2.9 Hz, 2 H, $H_{4,6}$), 7.35 (dd, J_{HCCH} = 8.4 Hz, J_{HCCOP} = 2.0 Hz, 2 H, $H_{arom.}$), 7.65 (d, 2 H, $H_{arom.}$); ^{13}C NMR: δ 22.2 (d, 2 C), 40.12 (d, 1 C), 76.66 (d, 2 C), 108.90 (s, 1 C),

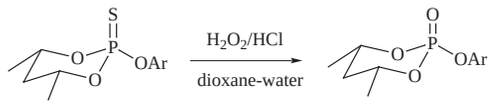
Table 2 Stereochemistry in the oxidation of *trans*-aryl thiophosphates (**1**–**7**) by H_2O_2–HCl



Ar	Thiophosphate, (δ ^{31}P)[a]	Oxo product, (δ ^{31}P)[a]	Stereoselectivity
p-$MeOC_6H_4$	**1**, (55.7)	**8**, (−12.2)	Retention
p-MeC_6H_4	**2**, (56.2)	**9**, (−13.8)	Retention
p-PhC_6H_4	**3**, (55.8)	**10**, (−12.6)	Retention
C_6H_5	**4**, (55.8)	**11**, (−12.7)	Retention
p-BrC_6H_4	**5**, (55.5)	**12**, (−13.1)	Retention
p-CNC_6H_4	**6**, (54.5)	**13**, (−15.0)	Retention
p-$NO_2C_6H_4$	**7**, (54.3)	**14**, (−13.7)	Retention

[a] Chemical shifts in ppm ($CDCl_3$).

Table 3 Stereochemistry in the oxidation of *cis*-aryl thiophosphates (**1**–**7**) by H_2O_2–HCl



Ar	Thiophosphate, (δ ^{31}P)[a]	Oxo product, (δ ^{31}P)[a]	Stereoselectivity
p-$MeOC_6H_4$	**1**, (61.0)	**8**, (−9.7)	Retention
p-MeC_6H_4	**2**, (60.9)	**9**, (−10.1)	Retention
p-PhC_6H_4	**3**, (60.4)	**10**, (−9.9)	Retention
C_6H_5	**4**, (60.2)	**11**, (−10.3)	Retention
p-BrC_6H_4	**5**, (60.1)	**12**, (−10.4)	Retention
p-CNC_6H_4	**6**, (59.4)	**13**, (−12.2)	Retention
p-$NO_2C_6H_4$	**7**, (59.2)	**14**, (−10.8)	Retention

[a] Chemical shifts in ppm ($CDCl_3$).

118.15 (s, 1 C), 121.24 (d, 2 C), 133.99 (s, 2 C), 153.91 (d, 1 C); MS: *m*/*z* 267 (M^+), 226 ($M^+ - 41$), 200 ($M^+ - 67$), 181 ($M^+ - 86$), 119 ($M^+ - 148$), 68 ($M^+ - 199$), 41 ($M^+ - 226$). Anal. Calcd for $C_{12}H_{14}O_4PN$: C, 53.92; H, 5.28. Found: C, 53.97; H, 5.42%.

r-2-(*p*-Nitrophenoxy)-2-oxo-*t*-4,*t*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*trans*-14)

Purification by flash column chromatography gave 0.070 g (73.7%) of a solid, mp 121–122 °C. The NMR spectral data for this compound are in agreement with those reported in the literature.[17,21]

r-2-(*p*-Nitrophenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-14)

Purification by flash column chromatography resulted in 0.030 g (31.6%) of a yellow oil (further recrystallization of this compound from hexanes should result in colorless crystals, mp 78–79 °C as described in the literature [17,20]). The NMR spectral data for this compound are in accordance with those reported previously.[17,21]

r-2-(*p*-Carboxyphenoxy)-2-oxo-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-15)

This compound was prepared from oxidation of *r*-2-(*p*-cyanophenoxy)-2-thio-*c*-4,*c*-6-dimethyl-1,3,2λ^5-dioxaphosphinane (*cis*-**6**) following the general procedure described above and changing the reaction time to 48 h. Recrystallization from ethyl acetate afforded 0.031 g (32.6%) of colorless crystals, mp 156–157 °C. ^{1}H NMR (acetone-d_6): δ 1.36 (dd, J_{HCCH} = 6.2 Hz, J_{HCCOP} = 1.8 Hz, 6 H, CH_3's at C_4 and C_6), 1.81 (dt, J_{gem} = 14.8 Hz, J_{anti} = 11.7 Hz, 1 H, H_5 *ax*.), 2.14 (dq, J_{gem} = 11.7 Hz, J_{gauche} = 2.8 Hz, J_{HCCOP} = 2.8 Hz, 1 H, H_5 *eq*.), 4.81 (m, 2 H, $H_{4,6}$), 7.36 (dd, J_{HCCH} = 8.4 Hz, J_{HCCOP} = 2.7 Hz, 2 H, $H_{arom.}$), 8.07 (d, 2H, $H_{arom.}$); ^{13}C NMR (acetone-d_6): δ 21.50 (d, 2 C), 39.33 (d, 1 C), 77.01 (d, 2 C), 120.09 (d, 2 C), 127.41 (s, 1 C), 131.50 (s, 2 C), 154.53 (d, 1 C), 166.05 (s, 1 C); ^{31}P NMR: δ −11.55; MS: *m*/*z* 286 (M^+), 245 ($M^+ - 41$), 219 ($M^+ - 67$), 201 ($M^+ - 85$), 183 ($M^+ - 103$), 68 ($M^+ - 215$), 41 ($M^+ - 245$). Anal. Calcd for $C_{12}H_{15}O_6P$: C, 50.34; H, 5.28. Found: C, 50.59; H, 5.44%.

Results

Stereospecific syntheses of epimeric thiophosphates **1**–**7** were performed as described elsewhere.[20]

The oxidation of thiophosphates was carried out in 1,4-dioxane by an aqueous solution of hydrogen peroxide (30%). Hydrogen chloride was used in the reaction to accelerate the attack of sulfur on hydrogen peroxide (see Scheme 1). The temperature and reaction times were kept constant for all the experiments. The stereoselectivity of the reaction was analyzed by ^{31}P NMR of the crude material (Tables 2 and 3).

From inspection of Tables 2 and 3, it is deduced that regardless of configuration and of the electronic characteristics of the aryloxy group, the oxidation reaction (which was followed by ^{31}P NMR of the crude material, see the Experimental section for details) proceeded in quantitative yields with high stereospecificity to give the oxo products with retention of configuration at the phosphorus center.

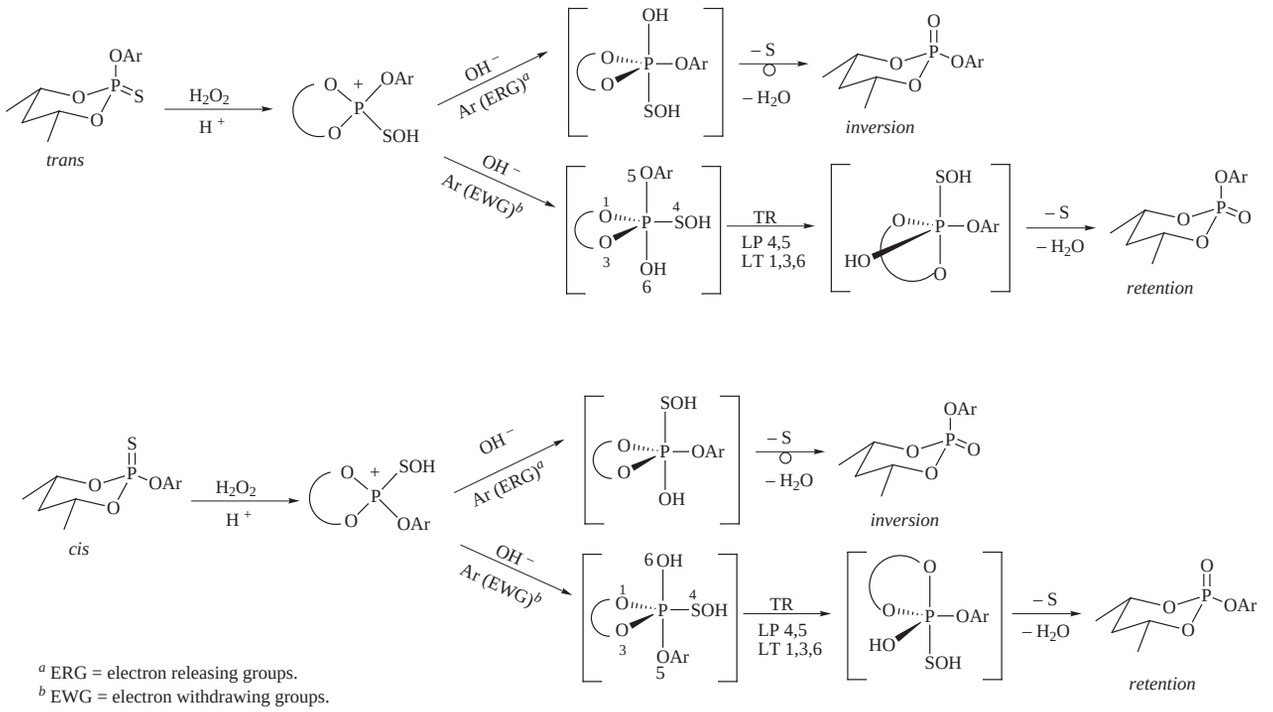
In the case of compound *cis*-**6**, the cyano group was also oxidized to the carboxy group to some extent, after 24 h of reaction. The oxidation of the cyano group was fully achieved at 48 h as indicated in the Experimental section of this work. See also the discussion below.

Discussion

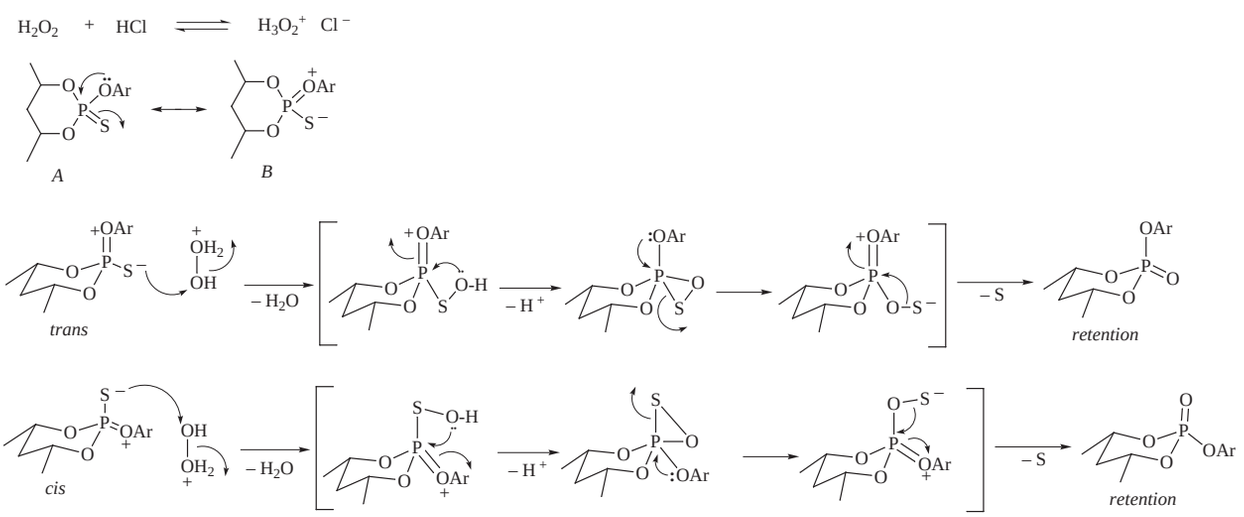
It is of importance to note that the fact that the oxidation was highly stereospecific for all the thiophosphates studied was unexpected. As stated above, there is a strong dependence of the electronic environment at the phosphorus atom and the stability of a pentacoordinate intermediate, thus it was anticipated that if the mechanism of the oxidation of epimeric *cis* and *trans* thiophosphates **1**–**7** by hydrogen peroxide (in hydrogen chloride) relies on pentacovalent intermediates (see proposed mechanism in Scheme 3), the stereochemical outcome should favor either an inversion or a retention process, but not only one (retention) as observed. The stereomutation of thiophosphates may be expected in long-lived pentacovalent intermediates in which pseudorotation is allowed. In other words, as shown in Scheme 3, retention of configuration would have been expected for electron withdrawing groups (X = NO_2, CN, Br) and inversion for electron releasing groups (OMe, Me, Ph).

Alternatively our results can be explained by proposing a concerted mechanism (Scheme 4) in which the *para*-substituents at the aryloxy group do not alter the stereochemical outcome but do affect the rate of the oxidation reaction. In particular, due to the likely participation of the mesomeric ionic structure (*B* in Scheme 4), an electron releasing group (ERG) in the aryloxy substituent is anticipated to increase the rate of oxidation, whereas an electron withdrawing group (EWG) is expected to decrease it. The stereochemistry of the thiophosphates, though, is not expected to change since in both cases the favored oxo product is the one that results from retention of configuration.

In this context, to support the proposed mechanism, we performed some oxidations-in-competition experiments (see the Experimental section for details) with thiophosphates **1**, **4** and **7** in both configurations, and the mixture hydrogen per-



Scheme 3



Scheme 4

oxide–hydrogen chloride in 1,4-dioxane. Here, we observed that the oxidation was indeed retarded by the nitro substituent but it was accelerated by the methoxy substituent (Table 4).

In addition, when the oxidation of the *p*-cyano thiophosphate **6** in the *cis* configuration was allowed to proceed for a longer period (48 h) the cyano group was fully converted into the carboxy group. However, the cyano group in the *trans* epimer was maintained without change after one month of reaction under the same oxidizing conditions. These results may be explained by envisioning that in the concerted mechanism (Scheme 4) the transition state resembles an ideal tetragonal pyramid geometry (TP) wherein the oxidizing agent and the cyano group are necessarily closer in the *cis*- (86°) than in the *trans*-isomer (105°).[23]

Finally, in order to study the scope of the methodology proposed here for the oxidation of the thiophosphates, we performed some experiments by using acetic acid as the protic medium. The results summarized in Table 5 indicate that the stereoselectivity of the oxidation reaction decreases. We think that this behavior reflects the differing abilities of the conjugated bases (Cl^- *vs.* CH_3COO^-) to stabilize the thiophosphonium intermediate which leads to the pentacoordinate species (Scheme 3).

Evidently, our results are in favor of a higher stabilized [$(RO)_3P^+SOH$, $^-O(CO)CH_3$] than [$(RO)_3P^+SOH$, ^-Cl] intermediate. Even though this hypothesis may perhaps be supported by results for oxidation of phosphoryl compounds in the literature,[7a,24] there is no doubt that further analysis of kinetic and stereochemistry results of the oxidation of aryl thiophosphates in different protic acid solutions is warranted. We are now working on the issue.

Conclusion

A highly stereospecific oxidation of cyclic six-membered thiophosphates **1**–**7** in their epimeric *cis* and *trans* forms was achieved using a cheap and commercially available solution of aqueous 30% hydrogen peroxide in hydrogen chloride, using 1,4-dioxane as solvent. The products were obtained with retention of configuration regardless of the stereochemistry of the starting thiophosphate. The lack of a dependence of the stereo-

Table 4 Oxidations-in-competition experiments with *cis*- or *trans*-aryl thiophosphates (**1**, **4** and **7**)

Thiophosphate	Reaction time/h	% of conversion[a]	Thiophosphate	Reaction time/h	% of conversion[a]
trans-**1**	0.12	1/0.36	*cis*-**1**	0.12	1/7.43
	0.18	1/1.63		0.18	[b]
	0.25	1/21.36			
	0.33	[b]			
trans-**4**	0.15	1/0.15	*cis*-**4**	0.13	1/0.38
	0.27	1/0.84		0.23	1/6.33
	0.37	1/4.00		0.32	1/167.36
	0.45	[b]		0.38	[b]
trans-**7**	0.25	1/0.04	*cis*-**7**	0.15	1/0.12
	0.48	1/0.11		0.42	1/0.27
	0.70	1/0.25		0.65	1/0.60
	0.92	1/0.49		0.90	1/1.02
	1.15	1/0.88		1.17	1/1.83
	1.38	1/1.62		1.40	1/4.29
	1.62	1/2.79		1.65	1/21.04
	1.85	1/8.83		1.88	[b]
	2.05	[b]			

[a] Values are the area ratio of ^{31}P NMR signals of thiophosphate/phosphate. [b] No starting material was detected.

Table 5 Stereochemistry in the oxidation of thiophosphates (**1**, **3**, **4**, **7**) by H_2O_2–CH_3CO_2H in 1,4-dioxane–water as solvent

Thiophosphate (series *cis*)	% of retention[a]	Thiophosphate (series *trans*)	% of retention[a]
1	74	**1**	86
3	75	**2**	89
4	82	**4**	84
7	100	**7**	100

[a] This percentage was calculated by means of the area ratio of the ^{31}P NMR signals of each oxo product in the crude material.

chemical outcome on the electronic characteristics at the phosphorus center, along with oxidation reactions in competition, support a concerted pathway as responsible for the oxidation mechanism.

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