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INVESTIGATIONS OF THE NUCLEOPHILIC DISPLACEMENT AT THE TETRAHEDRAL PHOSPHORUS - KINETIC EFFECTS OF THE NUCLEOPHILE FOR A GIVEN STEREOCHEMISTRY.[1]

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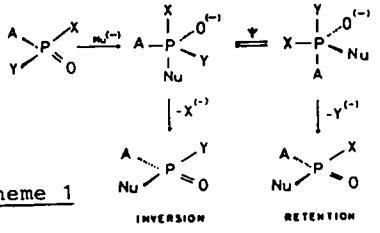
Abstract - A kinetic study of alcoholysis and aminolysis of 2-chloro-2-oxo-1,3,2-dioxaphospholane, 1, shows a rate levelling effect of the nucleophile, where the stereochemistry is retention at phosphorus. On the other hand, the substitutions with inversion of the 2-chloro-2-oxo-1,3,2-dioxaphosphorinane 2, or the diethylchlorophosphate, 3, show a marked influence of the nucleophile upon the reactivity. Furthermore, the large rate increase which has been observed for the hydrolysis of the five-membered ring phosphorus esters compared to phosphates (an oxygen always displaces an oxygen) is not reproduced when the leaving group is different of the nucleophile. We suggest that the mechanistic implications, established in the case of phosphate esters hydrolysis cannot be directly extended to the general case of $S_N2(P)$. The mechanism of nucleophilic substitution of P(4) species is better interpreted in terms of HOMO-LUMO interactions between the nucleophile and the substrate, a process now well established in silicon chemistry.

INTRODUCTION

The mechanism of $S_N2(P)$ displacement of the P-X bond (X = halogen, OR, SR...) of tetracoordinated species is commonly accepted to proceed through the initial formation of the P(5) intermediate of trigonal bipyramidal (tbp) geometry, with apical entry of the nucleophile.[2-4] The direct displacement of the leaving group ("in-line" attack) gives inversion at phosphorus. Retention at P is explained by the initial formation of a tbp structure with the attacking nucleophile in apical position and the leaving group in equatorial position ("adjacent" attack). Then, ligand reorganization (via pseudorotation or other) allows the apical departure of the leaving group with retention. The key finding of these interpretations is the initial formation of the more stable tbp structure in terms of the relative apicophilicity of the different substituents (Scheme 1).[5]



Scheme 1

A completely different interpretation has been considered at silicon to explain the stereochemistry of S_N2 (Si) reactions.[6] The stereochemistry, retention and/or inversion, is a direct function of the approach of the nucleophile in terms of HOMO-LUMO interactions between the two species. Front-side attack (90°) gives retention. Back-side attack (180°) gives inversion. Extensive studies upon the nucleophilic substitution of organosilanes allowed us to emphasize chief factors governing the stereochemistry at silicon i) the lability of the leaving group, ii) the electronic character of the nucleophile. Moreover, kinetic data showed the electronic factors to be essential in determining the geometry of the initially formed pentacoordinated intermediate. Ab initio calculations using an extension of Salem's orbital treatment of the Walden inversion have been performed.[7] On this basis, a new interpretation offered a simple and consistent way to rationalize all kinetic and stereochemical experimental facts of nucleophilic displacement at silicon.[8] Obviously, the mechanisms invoked in the two series Si, P are not comparable .

The main purpose of the present work corresponds to studies of structure - reactivity relationship between incoming nucleophiles and leaving groups for a given stereochemistry at phosphorus. As also already reported by Hall and Inch[4], Wadsworth[15] we have observed that the stereochemistry depends on the nature of nucleophile, leaving group and structure of the substrate. This points out the strong analogies between the stereochemistries of nucleophilic displacement of Si and P derivatives[9]. A further comparison was made concerning the endocyclic substitution of oxa (thia) silacycloalcanes, which emphasized the importance of the involved species upon the reactivity. The large rate increase (10^4) for the solvolysis of the five-membered ring compound[10] relative to the acyclic one is only observed when an oxygen nucleophile replaces an oxygen leaving group.

In the present paper, $S_N2(P)$ reactions have been checked, changing the nature of both the nucleophile and the leaving group. In order to compare more closely with the Westheimer's data, based upon the hydrolysis of phosphates and phosphonates, we have studied the nucleophilic displacement of P-Cl bonds with different nucleophiles in the case of five-membered ring, six-membered ring and acyclic chlorophosphates.[11]

RESULTS

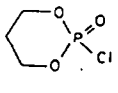
Kinetics

Organochlorophosphates are much more reactive than phosphates with alcohols. The nucleophilic substitutions of P-Cl bonds with amines are quantitative, compared to the reaction of phosphorus esters which give also the products of the attack at the adjacent carbon atom.[12] Kinetic experiments have been performed on 3 models : 2-chloro-2-oxo-1,3,2 dioxaphospholane, 1, 2-chloro-2-oxo-1,3,2 dioxaphosphorinane, 2, and 0,0-diethylchlorophosphate, 3.

Water, ethanol, phenol and diethylamine have been used as nucleophiles. Experimental conditions have been chosen in order to avoid secondary reactions, like formation of pyrophosphate, or ring cleavage of the five-membered ring phosphorus ester. The only particular case concerned the hydrolysis of 3, which gave tetraethylpyrophosphate (TEPP). Since the second step is faster than the first one (see experimental section) the rate constant value corresponds to the formation of phosphorus salt with P-Cl bond cleavage.

In all cases, the rate law is first order in chlorophosphate and first order in nucleophile. The rate constant values are reported in Table 1.

Table 1 : Second order rate constants for solvolysis of chlorophosphates (at 0°C in CH_2Cl_2).

Reactant	NuH	k $l.mole^{-1}s^{-1}$
	H_2O	0.20
	H_2O *	0.01
	EtOH	0.11
	PhOH	0.68
	Et_2NH	0.21
	EtOH	0.55×10^{-6}
	PhOH	0.29×10^{-3}
	Et_2NH	0.38×10^{-2}
$(EtO)_2P(O)Cl$	H_2O *	0.35×10^{-4}
	EtOH	0.12×10^{-5}
	PhOH	0.16×10^{-3}
	Et_2NH	0.28×10^{-1}

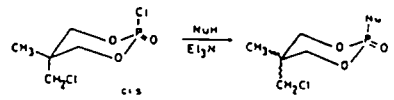
* solvent : CH_3CN

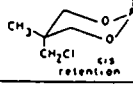
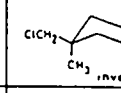
In the case of six-membered ring compound, 2, and acyclic derivative, 3, the k-values are highly dependent upon the nature of the nucleophile. Amines are much more reactive than alcohols ($k \simeq 10^4$). Such a difference is not observed in the case of strained 1. Very close rate constants are measured for various nucleophiles.

Stereochemistry

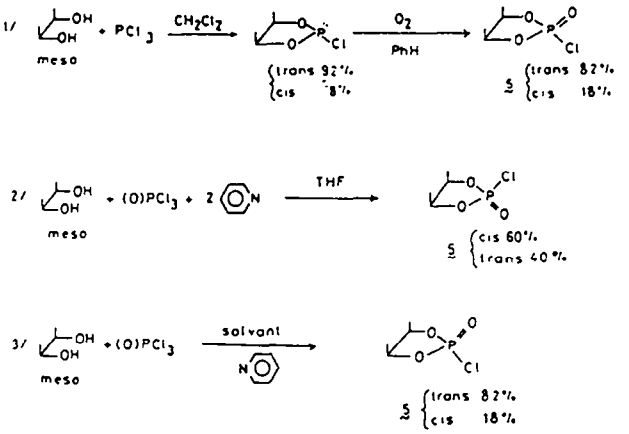
Nucleophilic displacements of acyclic phosphorochloridates have been shown to give inversion.[14] Wadsworth reported also inversion at phosphorus in the coupling reaction of methanol or amines with the 2-chloro-2-oxo-5-chloromethyl-5-methyl-1,3,2,dioxaphosphorinane.[15] We have reinvestigated that stereochemistry using ^{31}P NMR under our kinetic experimental conditions (Table 2). The essential feature is predominant inversion at phosphorus, whatever the nucleophile.

Table 2 : Stereochemical data of 4 with nucleophiles



NuH	 cis retention	 trans inversion
EtOH	δ = -8.1ppm 9.5 %	δ = -7.1ppm 90.5 %
	δ = -14.1ppm 17 %	δ = -13.2ppm 83 %
Et_2NH	δ = -8.8ppm 16 %	δ = -7.8ppm 84 %

Nucleophilic substitutions of five-membered ring thio-phosphorochloridates are known to proceed with retention at phosphorus.[16] The stereochemical studies have been extended to phosphorochloridates. The synthetic approach to the compounds is reported in scheme 2. For comparison, we have also prepared the thio derivative.



Scheme 2

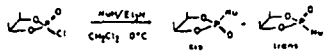
Treatment of 2,3-butanediol(meso) with PCl_3 gives the 2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane (92 % trans). The oxidation is stereoselective. The same predominant isomer is directly formed by coupling reaction of 2,3-butanediol(meso) with $(O)PCl_3$, in the presence of a large excess of pyridine. If only 2 equivalents of pyridine are introduced, the mixture contains the cis major isomer.[17]

The assignments as to cis and trans configurations of the phosphorochloridate 5 have been made on the basis of ^1H NMR chemical shifts data.[18] Protons in 1,3 cis position relative to P = O are shifted downfield, with also a different coupling constant (Table 3).

Table 3 : ^{31}P and ^1H NMR data of 2-substituted-2-oxo-4,5-dimethyl-1,3,2 dioxaphospholane, 5.

X		$\delta_P(CH_2Cl_2)$	$\delta_H CH_3(^3J_{HH})$	$\delta_H CH(^3J_{PH})$	others
Cl	cis	19.4	1.46(6)	5.03(12.9) 4.86(9.3)	
	trans				
OMe	cis	16.7	1.31(6.4)	4.63	$\delta_{OCH_3}(^3J_{PH})$ 3.77(12) 3.75(11.8)
	trans	15.3			
OEt	cis	14.8	1.36(8)	4.76	$\delta_{OCH_2CH_3}$ 1.36
	trans	13.5			
OPh	cis	8.45	1.36(6)	4.8	
	trans	7.16			
NEt_2	cis	21.6	1.38(6)	4.82(6) 4.65(12)	$\delta_{NCH_2CH_3}$ 1.12 $\delta_{NCH_2CH_3}$ 3.08(11)
	trans	22.1			

Table 4 : Stereochemical data of 5 with nucleophiles



	Nuc	cis	trans
85 % trans 72 % cis	NaOH	δ = 16.7 ppm 28 % 71 %	δ = 15.3 ppm 82 % 29 %
75 % trans 72 % cis	PhOH	δ = 8.5 ppm 25 % 69.5 %	δ = 7.2 ppm 75 % 30.5 %
75 % trans 72 % cis	Et_2NH	δ = 21.6 ppm 28 % 71.5 %	δ = 22.1 ppm 72 % 28.5 %

The stereochemistries of nucleophilic substitutions have been checked by means of ^{31}P NMR (Table 4). In the case of diethylamino coumpound, double resonance ^1H NMR technique confirms our assignments of the configurations. We note that the trans isomers present a ^{31}P chemical shift at higher field than the cis isomers. The same variation is observed in the case of the thio compound.[16]

Based upon our assignments of configuration, the main result is a change of stereochemistry, when we compare the six-membered ring compound 4 (predominant inversion) and the strained five-membered chlorophosphorus ester, 5, (retention).

DISCUSSION

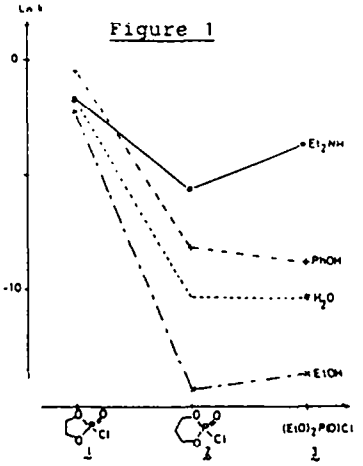
Kinetic results emphasize the difference in reactivity between five-membered ring compound, 1, and acyclic chlorophosphate, 3 (Table 5) :

Table 5

NuH	k_{C_5} / k_{ac}
H_2O *	3.4×10^2
EtOH	9×10^4
PhOH	4×10^3
Et_2NH	7.5

* solvent CH_3CN

Figure 1



The ratio between the second order rate constants is significantly high in the case of EtOH (10^5), compared to the reaction of diethylamine, for which the ratio fall down to 7.5. The influence of the nucleophile is even better illustrated in fig. 1, in which the rate constants are reported as a function of the geometry of the (P) reactant. In the case of the Et_2NH, close Ln k values correspond to a similar reactivity, whereas for EtOh, a large change of reactivity is exemplified. Meanwhile, we must note that the ratio of the rate constants k_{c5}/k_{ac} is very dependent upon the nature of the leaving group. For instance, the hydrolysis of the chloro compounds gives a ratio, k_{c5}/k_{ac} 3.4×10^2, much lower than the ratio k_{c5}/k_{ac} 10^6-10^8 observed in the case of hydrolysis of phosphate esters.

That means that the large kinetic effect which has been essential in the elaboration of the Westheimer's concepts is not confirmed in the case of different nucleophiles and different leaving group.

As a matter of fact , the present results reasses the question of the validity of the extension of these concepts to the generality of nucleophilic displacements at phosphorus. These were established in the case of the hydrolysis of P-O bonds, implying symmetrical intermediates (an oxygen displaces an oxygen). What we note, now, is that the large rate increase of five-membered ring compounds is no more a rule , as far as this symmetry disappears.

Table 6 (ref.10)

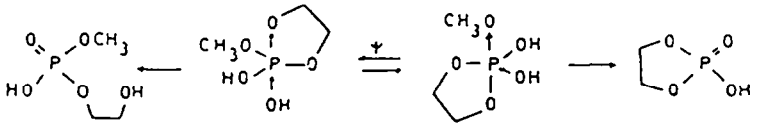
NuH			k_{rel}
H_2O (25°C)	30 1N	$3\ 10^5$ 1N	$5\ 10^3$
MeOH (25°C)	30 1N	$5\ 10^5$ 1N	$1.6\ 10^6$
MeLi (-78°C)	180 RN	600 RN	33
MeMgBr (20°C)	120 RN	300 RN	2.5
			k_{rel}
MeOH (15°C)	$3\ 10^3$ 1N	10^5 1N	33

Interestingly, the same conclusions have been already reached from the comparison of kinetic and stereochemical studies of hydrolysis and methanolysis of five and six-membered ring oxasilacycloalcanes. The predominant stereochemistry is inversion instead of retention, which is the normally expected pathway for the cleavage of Si-O bonds. The five-membered ring compound shows an enhanced reactivity. Such a rate increase is not observed when the incoming atom of the nucleophile is not an oxygen (i.e. carbon nucleophiles). These react at similar rates with five and six-membered ring oxasilacycloalcanes, whatever the stereochemistry.

The particular behaviour of oxasilacyclopentane is pointed out by hydrolysis and methanolysis of thiasilacyclopentane (Table 6). The displacement of the thio leaving group by an oxygen nucleophile corresponds to a reasonable increased reactivity due to angular constraint (t_{c6}/t_{c5} = 33).

In fact, the large rate increase is only observed when an oxygen displaces another oxygen, and this reaction takes place with inversion of configuration. This emphasizes the importance of symmetry between the leaving group and the incoming nucleophile in the tbp intermediate.

In the case of hydrolysis of phosphorus esters, only oxygenated species are involved. The phosphorus atom is surrounded by five oxygens. In such cases, the entering oxygen and the leaving oxygen have to be in apical positions, as proposed by Westheimer, and recently evidenced. The pentacoordinated intermediate always present the prosper geometry for activation (Scheme 3).



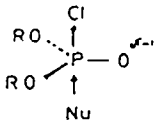
(Inversion) (Retention)

Scheme 3

In the present work, two cases are observed. Nucleophilic substitution of the five membered ring chlorophosphate 1, always proceeds with retention. The second order rate constants do not change with the nature of the nucleophile ($0.1 < k < 0.7$). On the other hand, in the case of diethylchlorophosphate, 3, for which the predominant stereochemistry would correspond to inversion at phosphorus, the rate constants considerably change with the nature of the nucleophile (Table 1). For example, the ratio of the rate constants for aminolysis and ethanolysis of 3 becomes $k_{R_2NH}/k_{EtOH} = 2 \times 10^4$.

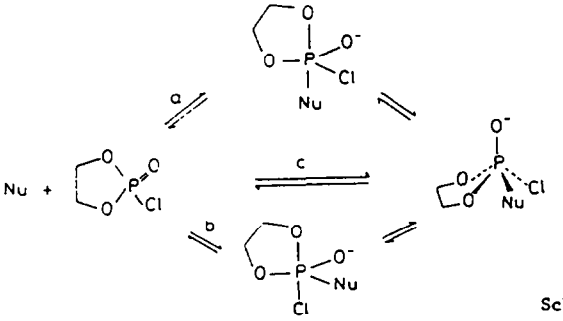
That means that for a given leaving group, the reactivity is strongly related to the stereochemistry of the substitution. In the reactions proceeding with retention (adjacent attack of Nu at 90° relative to the leaving group) the rate is quite independent upon the nature of the nucleophile. On the other hand, in the reactions proceeding with inversion (apical attack at 180° opposite to the leaving group) the rate is highly dependent on Nu (Fig 2). Such conclusions have been already reached in the case of nucleophilic substitutions at silicon. Therefore, the same explanations could apply. It is conceivable that, in an intermediate of tbp geometry, the stability is strongly dependent upon the mutual electronic interactions of the groups setting in apical positions.

Fig.2



Inversion (180°)

This is particularly evident for the inversion pathway. We observe a large rate increase depending upon the electronic character of Nu. At the opposite, in the case of retention (attack at 90°), three geometries could a priori account for the experimental facts : a) apical attack, b) equatorial attack, c) formation of a square pyramidal geometry. (Scheme 4)[21]



Scheme 4

At this moment, there is no definite argument allowing to decide between the three possibilities, which are of similar energies. Moreover the three structures can also rearrange by permutational isomerisations. The important point is that in these three configurations, the two

exchanging ligands stay orthogonal each other, which implies a "minimum" effect due to the incoming nucleophiles. In fact, if we considered, according to the Westheimer's proposals, the initial formation of the intermediate with apical attack of the nucleophile, we would also expect an extra-stabilisation of the O-atoms in diaxial positions, when the nucleophile is water or alcohol (Fig.3). Since experimentally, the chlorophosphate 1 reacts similarly with all the considered nucleophiles, oxygenated or not, the equatorial entry could be a more probable process, certainly through the formation of a square-pyramid (attack c on a face).

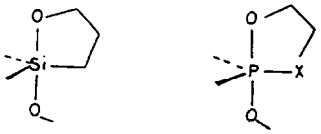


Figure 3

CONCLUSION

The experimental facts show that the hydrolysis of strained phosphate esters and perhaps any other reaction in which an oxygen displaces an oxygen can be considered as a special case since it behaves differently from the general case of nucleophilic displacement. For instance, the large rate increase which is observed for five-membered ring derivatives cannot be reproduced when the leaving group is different of the nucleophile, both in P and Si chemistry.

Therefore, it appears difficult to directly extend the Westheimer's concepts, established in the case of the hydrolysis of strained five-membered ring phosphates to the general case of nucleophilic substitutions at P(4) species.

On the other hand, the structure-reactivity relationship between incoming nucleophiles and leaving groups is highly dependent upon the stereochemical behaviour at phosphorus. The "in line" attack (180°) giving inversion corresponds to large interactions between the nucleophile and the leaving group : the influence of the nucleophile is essential ($\Delta k = 10^4$). At the opposite, in the adjacent process (attack at 90° giving retention), we note a levelling effect of the orthogonal exchanging ligands. The same results were previously noted for nucleophilic substitutions of organosilicon compounds[22]. They emphasize the analogy between the two series.

EXPERIMENTAL

Reactions were carried out in Schlenk tubes under dry N_2 - ^1H NMR spectra were recorded on Varian EM 360 or EM 390 instruments with TMS as internal reference. ^{31}P NMR spectra were measured at 32.37 MHz on a Fourier Transform Brucker WP 80. Positive chemical shifts are downfield relative to external 85 % H_3PO_4 diluted in D_2O (lock signal).

Reactants

Some compounds are prepared according to literature, 2-chloro-2-oxo-1,3,2-dioxaphospholane, 1.[24] 2-chloro-2-oxo-1,3,2-dioxaphosphorinane, 2,[23] diethylchlorophosphate, 3,[24], 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinane, 4,[15].
They present the structural features in ^{31}P NMR (CH_2Cl_2). 1, δp + 22.2 ppm ; 2, δp - 2.7 ppm ; 3, δp - 3.10 ppm ; 4, δp - 3.16 ppm.

2-chloro-4,5-dimethyl-2-oxo-1,3,2-dioxaphospholane, 5

Addition of 2,3 butane diol (meso) to trichlorophosphine in dichloromethane according to Lucas,[25] leads predominantly to trans 2-chloro-4,5-dimethyl-1,3,2-dioxaphospholane. Then, oxidation in benzene affords the title product, 5.
$b_{P(0.35)}$ 87°C, δ_H ($CDCl_3$) 1.46 ppm (d, 6H) 4.93 ppm (m, 2H). 4.86 ppm ($^3J_{P-H}$ 12.9 Hz, ~15 %). δp (CH_2Cl_2) = 19.4 ppm Mass spectrum : m/e M^+ 170 Found : C, 28.18 ; H, 4.64 ; P, 18.15 ; Cl, 20.62 $C_4H_8O_3PCl$ Required : C, 28.15 ; H, 4.69 ; P, 18.18 ; Cl, 20. 82 %.

The same product is obtained by dropwise addition of trichlorophosphine (0.015 mole) at 0°C to a solution of butane-2,3-diol meso (0.015 mole) in excess pyridine (15 ml) with stirring for 1h.
Then filtration of the pyridinium salt and evaporation of excess pyridine in vacuo leads to trans 5. 5H ($CDCl_3$) 4.86 ppm 75 %, 5.03 ppm 25 %.

Predominant cis 5 is obtained by dropping at 0°C a solution of butane-2,3-diol meso (0.0157 mole) and pyridine (0.0314 mole) in THF (5 ml) to a solution of trichlorophosphate (0.0157 mole) in THF (10 ml) and then usual work-up. δ_H($CDCl_3$) 4.8 ppm ($^3J_{P-H}$ = 9.3 Hz) 30 % 5.03 ppm ($^3J_{P-H}$ = 12.9 Hz) 70 %. δp (CH_2Cl_2) = 19.4 ppm

2-chloro-4,5-dimethyl-2-thio-1,3,2-dioxaphospholane cis and trans were prepared according to Lowe[23].
$\delta_H(CDCl_3)$ cis 4.90 ppm (m, 2H) 1.46 ppm (d, 6H)
$\delta_H(CDCl_3)$ trans : 4.90 ppm (m, 2H) 1.42 ppm (d, 6H)
$\delta_p(CH_2Cl_2)$ cis : 77.68 ppm, trans : 76.02 ppm

Products

The general procedure is described.
A solution of nucleophile (0.05 mole) and triethylamine (0.05 mole) in dichloromethane (5ml) is dropped to a solution of appropriate chlorophosphate (0.05 mole) in dichloromethane (10 ml). After stirring for 2 h, the solvent is removed. Benzene (10 ml) is added to the residue in vacuo. The salt is filtered off and benzene is removed.

Substitutions of 1

NuH = MeOH δ_H ($CDCl_3$) 3.9 ppm (d, 3H, $^3J_{CH_3P}$ = 14 Hz)
4.52 ppm (m, 4H). δp (CH_2Cl_2) = 18.1 ppm.
NuH = EtOH δ_H ($CDCl_3$) 1.37 ppm (t, 3H), 4.50 ppm (m, 6H), δp (CH_2Cl_2) = 17.1 ppm
NuH = PhOH δ_H ($CDCl_3$) 4.3 ppm (m, 4H), 7.23 ppm (m, 5H), δp (CH_2Cl_2) = 11.5 ppm
NuH = Et_2NH δ_H ($CDCl_3$) 1.16 ppm (t, 6H), 3.10 ppm (m, 4H), 4.33 ppm (m, 4H) δp (CH_2Cl_2) = 26.27 ppm.
In the case of hydrolysis of 1, two equivalents of triethylamine were used. $\delta_H(D_2O)$1.1 ppm (t, 9H) 3.0 ppm (q, 6H), 4.1 ppm (d, 4H, $^3J_{P-H}$ = 10 Hz) δp (CH_3CN) = 16.6 ppm.

Substitutions of 2

NuH = PhOH δ_H ($CDCl_3$) 1.80 ppm (m, 2H). 4.42 ppm (m, 4H), 7.32 ppm (s, 5H) δp (CH_2Cl_2) = -13.5 ppm
NuH = Et_2NH δ_H ($CLCl_3$) 1.13 ppm (t, 6H), 1.90 ppm (m, 2H), 3.19 ppm (m, 4H), 4.45 ppm (m, 4H), δP (CH_2Cl_2) = + 6.8 ppm
NuH = EtOH A large excess of ethanol (10 equivalents) is necessary to obtain the product in quantitative yield.
δ_H ($CDCl_3$) 1.4 ppm (t, 3H), 2.0 ppm (m, 2H), 4.3 ppm (m, 6H), δ_p (CH_2Cl_2) = - 7.3 ppm.

Substitutions of 3

NuH = PhOH δ_H ($CDCl_3$) 1.3 ppm (t, 6H), 4.2 ppm (m, 4H), 7.37 ppm (m, 5H). $\delta_P(CH_2Cl_2Cl_2)$ = -6.5ppm
NuH = Et_2NH δ_H ($CDCl_3$) 1.10 ppm (t, 6H), 1.30 ppm (t, 6H), 3.07 ppm (m, 4H), 3.97 ppm (m, 4H),
δ_P (CH_2Cl_2) 10.03 ppm
NuH = EtOH - A large excess of ethanol is necessary (10 eq.). δ_H ($CDCl_3$) 1.43 ppm (t, 9H),
4.16 ppm (m, 6H), δ_p (CH_2Cl_2) - 1.08 ppm
NuH = H_2O - Tetraethylpyrophosphate (TEPP) is obtained instead of the triethylammonium salt of diethylphosphoric acid.
δ_H ($CDCl_3$) 1.40 ppm (t, 12H), 4.26 ppm (m, 8H), $\delta_p(CH_3CN)$ = - 13.54 ppm

Preparation of diethylphosphoric acid

3 (0.018 mole) is dissolved in hot water (15 ml). Extraction with chloroform (4 x 20ml) gives diethylphosphoric acid (0.011 mole). δ_H ($CDCl_3$) 1.36 ppm (t, 6H), 4.13 ppm (m, 4H), 11.7 ppm (s, 1H) δ_P (CH_2Cl_2) 0 ppm. After addition of excess Et_3N δ_P (CH_2Cl_2) = 1.73 ppm.

Preparation of tetraethylpyrophosphate

A solution of 3 (2.4 mmoles) in acetonitrile (1 ml) is added to a solution of diethylphosphoric acid (2.4 mmoles) and triethylamine (2.4 mmoles) in acetonitrile (1 ml). Triethylammonium chloride deposites quickly. After filtration and evaporation of the solvent TEPP is obtained in quantitative yield.

Stereochemistry

The substitutions of 4 and 5 follow the same procedure than that for 1 and 2. Stereochemistry is attributed by means of ^1H NMR and/or ^{31}P NMR. The results are reported in Tables 2,4.

Kinetics

Dichloromethane is distilled over P_2O_5 under nitrogen. Acetonitrile is dried by successive distillations (x 3) over P_2O_5. Amines are refluxed over KOH in pellets before distillation. Methanol and ethanol are distilled over magnesium methoxide and magnesium ethoxide, respectively.

Kinetics method

The rates are measured by acidimetry. Aliquots of the reaction mixture (5 ml) are run at -20°C into dichloromethane (25 ml), and a solution of chlorhydric acid in toluene is added. The amount of chlorhydric acid is calculated to be equal to the initial amount of the amine in the sample. The excess of acid is quickly back titrated with a standard solution of triethylamine in toluene with neutral red as indicator.

Kinetics measurements

All kinetics runs were performed at 0°C in ice bath. Two procedures were used depending on the rate of the reaction. For a slow reaction the mixture of triethylamine and nucleophile in dichloromethane (25 ml) is added (at 0°C) (t = 0) to a solution of chlorophosphate in dichloromethane (25 ml) at 0°C. Aliquots (5 ml) are titrated at various intervals. For fast reactions, 2.5 ml of each solution are mixed and the same procedure applied. Second order rate constants were calculated from the equation 2 where a and b are the initial concentrations of phosphorochloridate and nucleophile and x is the concentration of HCl at time t. For the hydrolysis of 3, a different equation was necessary (eq.3).

eq. 2 $k_2 t = \frac{1}{b-a} \text{ Log } \frac{a(b-x)}{b(a-x)}$ eq.3 $k_2 t = \frac{1}{b-a} \text{ Log } \frac{a(b-x)}{b(a-2x)}$

Table 7 - Experimental rate orders , at 0°C
(concentrations in mol.l^{-1})

Nu H	[]	[Nu H]	[Et_3N]	k order 2 $l mole^{-1} s^{-1}$	k order 3 $l^2 mole^{-2} s^{-1}$
EtOH	0.01	0.01	0.01	0.12	18.6
	0.01	0.01	0.03	0.10	3.8
	0.10	0.10	0.10	0.14	1.8
	0.05	0.05	0.05	0.09	2.1
	0.20	0.20	0.20	0.10	1.3
PhOH	0.10	0.10	0.20	0.70	44.0
	0.10	0.10	0.10	0.72	12.6
	0.05	0.05	0.05	0.64	16.1
Et_2NH	0.10	0.20	0	0.24	5.36
	0.10	0.10	0.10	0.24	4.50
	0.05	0.05	0.05	0.19	4.80
H_2O (CH_3CN)	0.10	0.10	0.20	0.049	0.41
	0.10	0.20	0.20	0.053	0.41
	0.01	0.01	0.02	0.043	2.41
H_2O (CH_2Cl_2)	0.01	0.1	0.20	0.20	1.11
	0.01	0.01	0.10	0.21	2.10

	[]	[Nu H]	[Et_3N]	k order 2 $l mole^{-1} s^{-1}$	k order 3 $l^2 mole^{-2} s^{-1}$
EtOH	0.1	5	0.1	0.6×10^{-6}	7.2×10^{-6}
	0.1	10	0.1	0.5×10^{-6}	6.9×10^{-6}
PhOH	0.10	0.10	0.10	2.9×10^{-4}	6.4×10^{-3}
Et_2NH	0.10	0.10	0.10	3.8×10^{-3}	0.11

	$[(EtO)_2P(O)Cl]$	[Nu H]	[Et_3N]	k order 2 $l mole^{-1} s^{-1}$	k order 3 $l^2 mole^{-2} s^{-1}$
EtOH	0.1	5	0.1	1.0×10^{-6}	1.3×10^{-5}
	0.1	10	0.1	1.5×10^{-6}	2.1×10^{-5}
	0.2	10	0.2	1.3×10^{-6}	1.2×10^{-5}
PhOH	0.1	0.1	0.2	1.68×10^{-4}	8.9×10^{-4}
	0.1	0.1	0.1	1.50×10^{-4}	2.6×10^{-3}
Et_2NH	0.10	0.20	0	0.030	0.62
	0.01	0.02	0	0.011	5.41
	0.01	0.04	0	0.030	0.89
	0.01	0.01	0.01	0.029	3.85
	0.01	0.01	0.03	0.032	1.50
	0.05	0.05	0.05	0.023	0.71
	0.10	0.10	0.10	0.028	0.93
H_2O (CH_3CN)	0.10	1.00	0.40	3.6×10^{-5}	0.83×10^{-5}
	0.10	1.00	0.20	3.4×10^{-5}	2.01×10^{-5}
	0.10	0.50	0.20	3.5×10^{-5}	1.98×10^{-6}

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