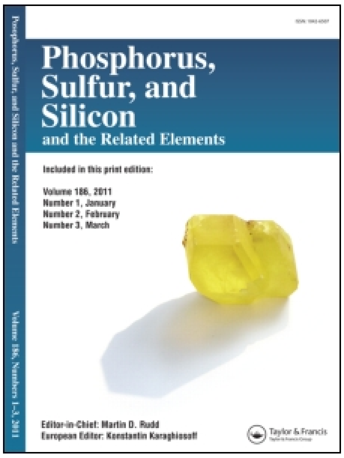

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SILICON-PHOSPHORUS ANALOGIES THE MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT SILICON AND PHOSPHORUS ACTIVATED BY EXTERNAL NUCLEOPHILES EXTENSION OF COORDINATION OF THE REACTIVE SPECIES

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SILICON-PHOSPHORUS ANALOGIES THE MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT SILICON AND PHOSPHORUS ACTIVATED BY EXTERNAL NUCLEOPHILES EXTENSION OF COORDINATION OF THE REACTIVE SPECIES

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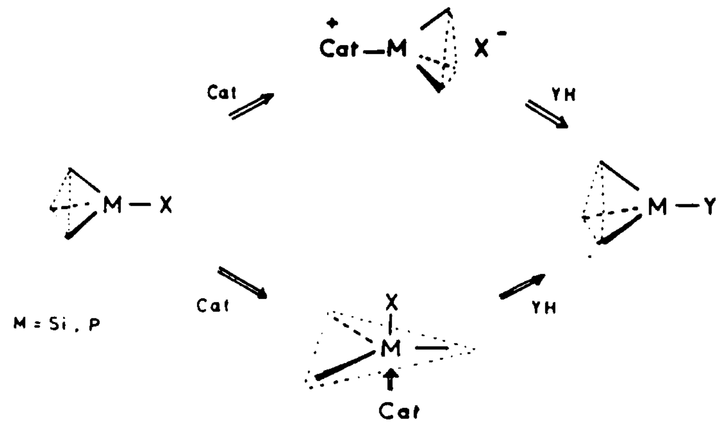
A comparison is made concerning the mechanism of S_N2 reactions of silicon and phosphorus compounds, catalyzed by nucleophiles. The rate-law of the catalyzed solvolysis of halogenophosphorus esters corresponds to a mechanism with extension of coordination of the reactive species. The overall inversion observed with chlorophosphonates affords a distinction between a nucleophilic activated substitution SN_{NA} (P) and a nucleophilic double displacement at phosphorus.

In his conference, R. Corriu presented the general aspects concerning the comparison between silicon and phosphorus compounds, and from both kinetic and stereochemical data, he concluded that the same rules may apply in the two series to explain the mechanism of nucleophilic substitution on the hetero-atom.[1]

In the present talk, I would like to focus the discussion on the particular case of nucleophilic substitution of Si, P compounds, catalyzed by the nucleophiles.[2]

What is the problem?



M(5) sterically hindered
negatively charged

Several reactions in the two series are known to be greatly accelerated by adding nucleophilic catalysts in the medium, and the usefulness of such processes has been extensively developed for synthetic purposes. However, from a mechanistic point of view, an important question remained unanswered: what is the nature of the catalytic species:[3] Is it a tetracoordinated ionic intermediate, corresponding to the replacement of X by an even better leaving group -Cat$^{(+)}$, which then reacts with YH in a second S_N2 reaction, or does the mechanism simply go through a pentacoordinated intermediate which is able to direct further substitution via an hexacoordinated transition state and/or intermediate?[4]

The question has been debated for a long time, and the main arguments which are presented against the formation of hexacoordinated transition states are:

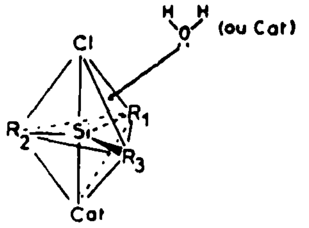
i) the attack on a pentacoordinated species would be sterically hindered, compared to the attack on a four coordinated species.

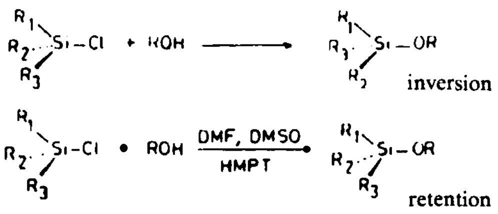
ii) the extra-coordination induces a formal negative charge on the central heteroatom, precluding the approach of the nucleophilic reagent.

Solvolytic reactions of silicon chlorides are important because of their practical use to obtain siloxanes or alkoxysilanes which are precursors for silicones, and similarly, phosphorus chlorides are useful as starting materials for pesticides, insecticides, etc....

The more efficient and selective catalysts are the dimethylaminopyridine (DMAP) and *N*-methylimidazole (NmI), even in the conditions of phase transfer catalysis.[5] Generally, the authors proposed the double displacement process as the more reasonable scheme to explain their kinetic data.

However, our group has been for a long time concerned with the problem of nucleophilic assisted racemization of chlorosilicon derivatives.[6] The observed third order reaction (order one in chlorosilane, and order two in catalyst) was explained by the initial formation of a pentacoordinated species, which then reacts with a second molecule of nucleophilic catalyst to form either an hexacoordinated species or a pentacoordinated siliconium ion. Further studies on the catalyzed hydrolysis of chlorosilanes showed this mechanism to be a general pattern. Both, the rate law and the activation parameters agree with the nucleophilic activated substitution process.[7]

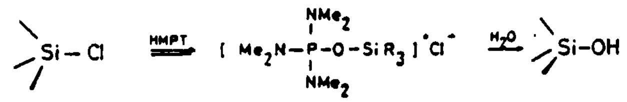




An important point was the observed stereochemistry. The catalyzed hydrolysis gives retention at silicon, instead of inversion which is the stereochemistry for non-catalyzed hydrolysis.

This result allowed Chojnowski and coll. to propose the double displacement scheme as the more reasonable pathway to explain the stereochemistry (2 inversions = 1 retention). These authors showed the formation of ionic species from the coupling mixture of Me_3Si X and HMPT.[8]

Ionic Process



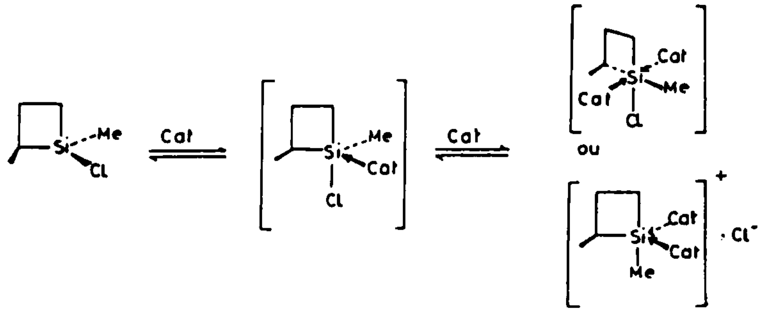
Similar ionic species have been evidenced with pyridine[9], DMF[10] or NmI[11].

However, it must be noted that these species are observed only in the case of extremely labile substituents. The system Me_3SiCl-Cat gives no definite answer to the formation of an ionic adduct.

On the other hand, conductimetric titrations argue against the hypothesis of ionic species. The observed conductance is lower than the value which could be due to HCl formed by hydrolysis with residual water in organic solvents.[12]

The last argument which can be considered against the double displacement mechanism concerns the behaviour of chlorosilacyclobutanes.[13] Cartledge *et. al.* noted the participation of two moles of catalyst in the process of racemization of these strained four-membered ring compounds.

The observed stereochemistry for S_N2 reactions of these silanes is always retention. That means that the double displacement process cannot explain the racemization scheme. On the other hand, we can imagine the formation of a quasi-symmetric pentacoordinated structure.



The kinetic data observed by Cartledge were also relevant.

At this moment, the conclusion we can make concerning the S_N2 (Si) reaction is that, despite the fact that no definitive choice can be made, the results argue mostly against the double displacement process. Meanwhile, and of themselves, they give us better confidence in our view that direct substitution on a pre-formed pentacoordinated complex or extension of coordination to give a hexacoordinated intermediate and/or transition state is consistent with kinetic and stereochemical data.

The question has been "debated" for a long time in a similar way for phosphorus compounds.[14] Two possibilities could arise.

1. Double displacement.

$$\gt\mathrm{P(O)X} \xrightleftharpoons[-X^{-}]{\mathrm{Cat}} \gt\mathrm{P(O)Cat^{+}} \xrightleftharpoons{\mathrm{NuH}} \gt\mathrm{P(O)Nu} + \mathrm{HX}$$

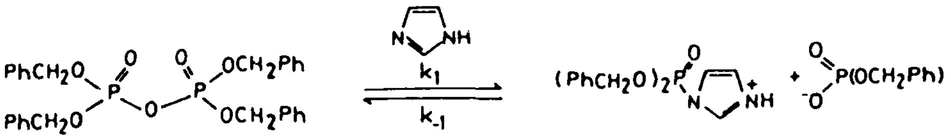
P(4) P(4′) P(4″)

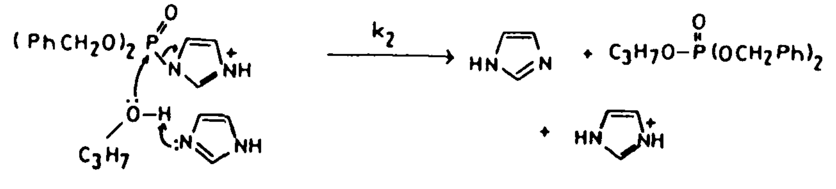
2. Nucleophilic assisted substitution.

$$\gt\mathrm{P(O)X} \xrightleftharpoons{\mathrm{Cat}} \gt\mathrm{P(O)XCat} \xrightleftharpoons{\mathrm{NuH}} \gt\mathrm{P(O)X\,CatNuH} \rightleftharpoons$$

P(4) P(5) P(6)

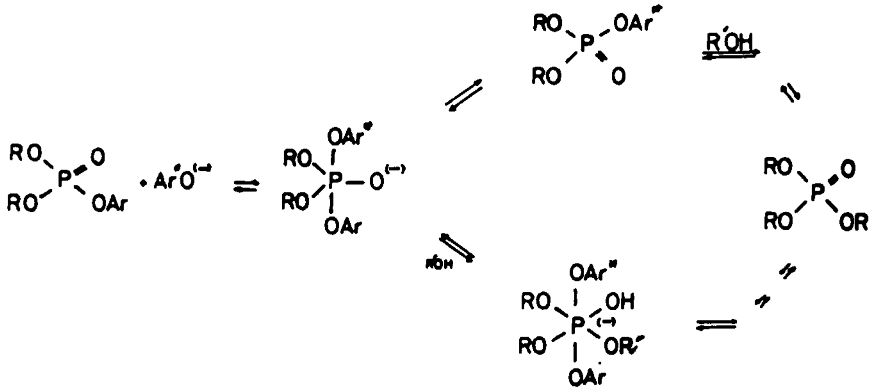
There are many examples of nucleophilic substitutions of phosphorus compounds, activated by nucleophilic catalysts. Generally, the authors envisage the formation of an ionic more reactive intermediate. The results presented by Westheimer in the case of the *n*-propanolysis of tetrabenzyl pyrophosphate (TBPP), catalyzed by imidazole (Im) are significant.[15] This author supposes that Im reacts with TBPP to form a



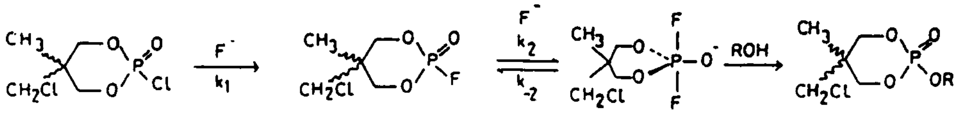


phosphorylimidazolium species, which then reacts in a second step with *n*-propanol to give the phosphate ester.

Two arguments are presented: i) the phosphorylimidazolide is also very reactive in these conditions. ii) an excess of dibenzyl phosphate anion decreases the rate of substitution (common ion effect). Another process of nucleophilic activation has been recently considered. To explain the auto-catalyzed solvolysis of *p*-nitrophenoxy phosphorus esters with *p*-nitrophenoxide anions, Ramirez envisaged the existence of penta- and hexacoordinated intermediates able to rearrange before departure of the leaving groups.[16]



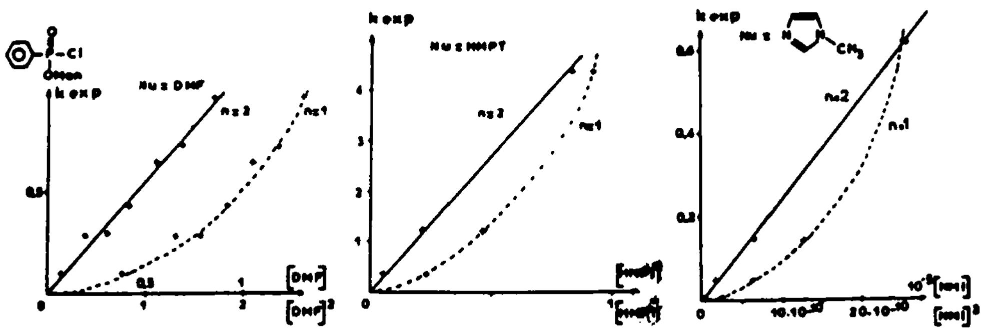
The fluoride activation of nucleophilic substitution at tetrahedral phosphorus offers another example of participation of external nucleophiles in $S_N2(P)$ reactions.[17]



The lack of stereoselectivity with the nature of the alcohol is attributed to the formation of a quasi-symmetrical phosphoranoxide species, much more reactive than the starting material.

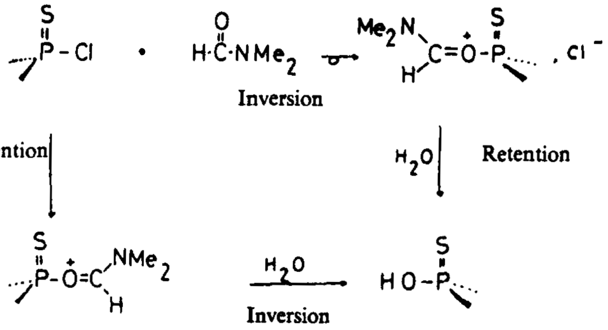
In order to compare the two series, chlorosilicon and chlorophosphorus species from the point of view of nucleophilic activation to nucleophilic substitution on the hetero-atom, we have first considered the process of nucleophilic induced racemization of chlorophosphorus derivatives.[2,18]

As for silicon compounds, we observe order three reactions with highly negative entropic values.

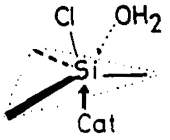


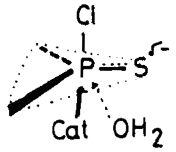
Similarly, the nucleophilic induced hydrolysis corresponds to the formation of well-organized intermediates.[19]

The essential point is the change of stereochemistry. The activated hydrolysis of chlorosilane gives retention. The activated hydrolysis of ethyl (phenyl) chlorothiophosphonate gives inversion. This result is difficult to rationalize from the consideration of the two consecutive steps in the double displacement mechanism. One of them would give the unlikely supposition of retention for $S_N2(P)$ of a phosphonate species.



On the other hand, if we consider the out of plane approach of the nucleophile on the pentacoordinated species, front-side attack would give retention, and back side attack inversion.

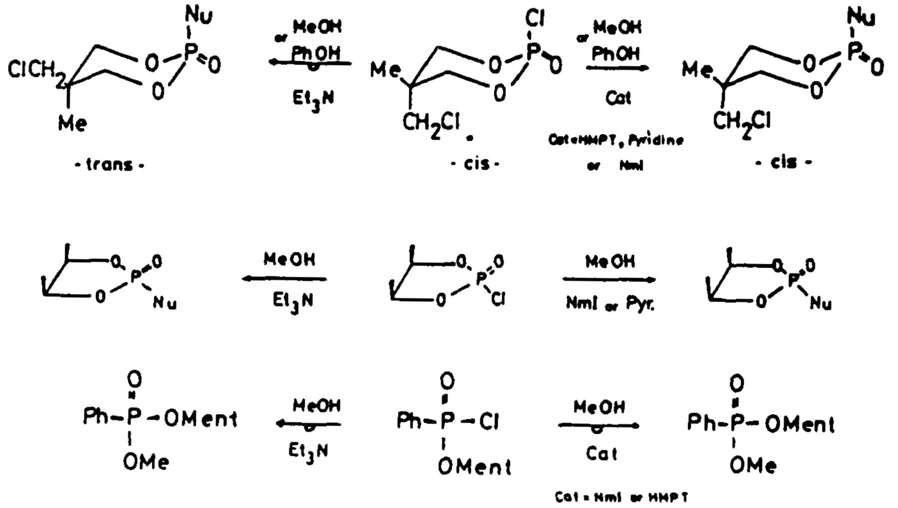




(An approach of the second molecule of Cat in the equatorial plane could not explain the racemization of the chlorophosphorus derivative in the absence of water).

We have generalized this study to phosphoro derivatives, with different nucleophiles, alcohol or phenol.

Stereochemistry



In the case of phosphoro compounds, six-membered ring derivatives, 1,3,2 dioxaphosphorinanes, or five-membered ring 1,3,2 dioxaphospholanes, we observe overall retention at phosphorus.

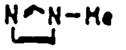
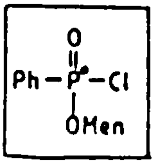
In the presence of Et_3N, the methanolysis of the five-membered ring chlorophosphate corresponds also to retention, but the 2-chloro 1,3,2 dioxaphosphorinane gives inversion.[20]

The catalyzed methanolysis of chlorophosphonates proceed with inversion.

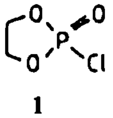
Kinetic experiments have been also performed with both phosphono and phosphoro derivatives. The experimental rate law depends on the whole system P/cat/NuH/Solv.

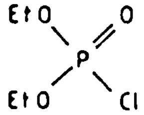
Some examples are given in the next table.

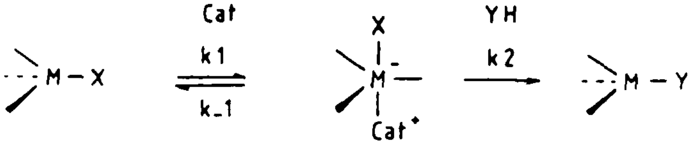
Inversion (phosphonates)

	EtOH / 	$v = k[P][Cat]$ (order 2)	$k = 1.15\ l.mol^{-1}\ s^{-1}$
	MeOH / HMPT	$v = \frac{k[P][Cat][ROH]}{1 + k'[ROH]}$ (complex order)	$k = 4.3 \times 10^{-3}\ l^2.mol^{-2}.s^{-1}$ $k' = 3\ l.mol^{-1}$
			$k\ (l^2\ mol^{-2}\ s^{-1})$
	H_2O / DMF	$v = k[P][Cat][ROH]$	2.7×10^{-3}
	H_2O / HMPT	(order 3)	1.0×10^{-3}

Retention (phosphates)

				$k\ (l.mol^{-1}\ s^{-1})$
 **1**	″	(order 2)	**1**	0.3
	EtOH / NmI / CH_2Cl_2	$v = k[P][Cat]$	**2**	0.1

			k	k'
 **2**	EtOH / Pyr / CH_2Cl_2	$v = \frac{k[P][Cat][ROH]}{1 + k'[ROH]}$ (order complex)	9×10^{-2}	15
	″ / HMPT / ″		4.5×10^{-4}	20
	EtOH / NmI / CH_3CN		23.6	35



(Bodenstein)

$$v = \frac{k1 \frac{k2}{k_{-1}} [MX][Cat][YH]}{1 + \frac{k2}{k_{-1}} [YH]}$$

if $\frac{k2}{k_{-1}} \ll 1$

$$v = k1 \frac{k2}{k_{-1}} [MX][Cat][YH]$$

if $\frac{k2}{k_{-1}} \gg 1$

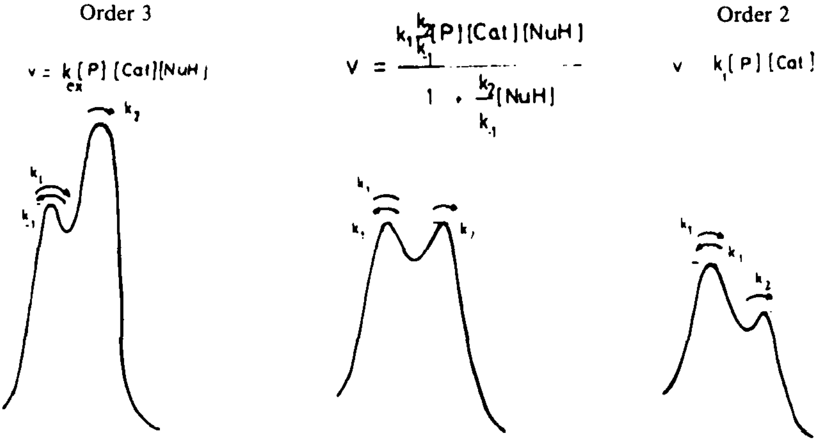
$$v = k1 [MX][Cat]$$

A tentative rationalization of these apparently not fully coherent rate orders may be obtained from the consideration of the Bodenstein state approximation.

The rate equation can be simplified, depending on the value of the ratio k2/k − 1. If this ratio is small compared to 1, the apparent third order reaction corresponds to the situation which has been observed, for example, in the case of the hydrolysis of chlorophosphonates. If k2/k − 1 ≫ 1, which is equivalent to saying that the second step is faster than the reverse reaction to the starting material, the apparent rate law corresponds to an order two reaction. This is generally the case with the very efficient catalyst, NmI.

In other cases, we observe a complex rate law which fits the constant values on a large scale of experimental data.

We have tentatively assigned the reaction profile for the different possibilities, depending on the ratio k2/k − 1. There is a "continuum" in the variation of the overall process.



ex. PhP(O)ClOMen/H_2O/DMF ex. PhP(O)ClOMen/MeOH/HMP† ex. PhP(O)ClO;Pr/MeOH/NmI
$(EtO)_2POCl$/EtOH/Pyr/CH_2Cl_2 $(RO)_2P(O)Cl$/ROH/NmI
/NmI/CH_3ON

the second step is even more accelerated than the initial formation of the pentacoordinated intermediate.

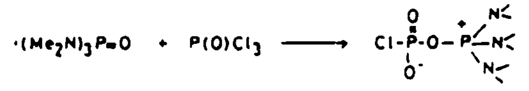
We must note that "the second step is even more accelerated than the initial formation of the pentacoordinated intermediate".

That remark was already pointed out by Cartledge, who also observed a change of the apparent rate law, for the racemization of chlorosilacyclobutanes. From the reported data, we could calculate a ratio $k2/k1 \neq 10^2$. But the racemization studies have been performed with smaller ranges of concentrations (10^{-5}–10^{-3}M in HMPT).[13]

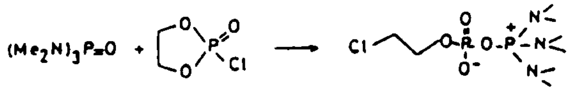
At this point, I have to put forward some additional argumentation against the formation of ionic intermediates, since, as I have shown, despite the fact that there is no evidence for such species in the case of chlorosilanes, similar ionic compounds have been characterized with better leaving groups.

Westheimer reported a common ion effect in the alcoholysis of tetrabenzyl pyrophosphate, catalyzed by imidazole.[15] We do not observe such a decrease of the rate by adding Cl^- anions in the medium. In fact, what we note is a small increase of the rate, which can be attributed, as with perchlorate anion, to modification of the ionic strength of the medium.

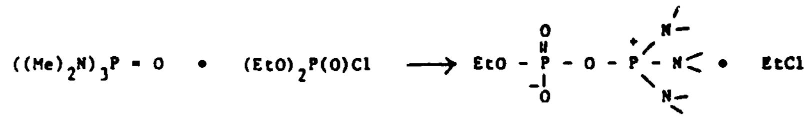
The Wilsmaier reagent, $OPCl_3$ + DMF, has been studied for a long time.[21] Castro and Dormoy reported the formation of betaines from HMPT with $OPCl_3$. Similarly ^{31}P nmr spectrum of the 1/1 adduct of HMPT and diethyl chlorophosphate shows two new signals at −13 ppm and +26.4 ppm which can be attributed to the betaine structure.[22]



$\delta = -18$ ppm $\delta = +26$ ppm
$J_{PP} = 25.5$ Hz

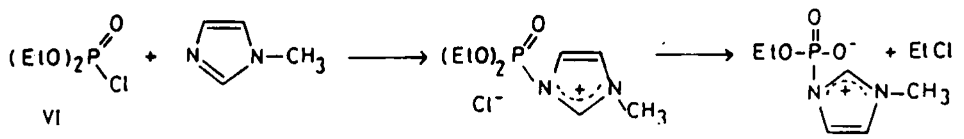


$\delta = -10.1$ ppm $\delta = +26.4$ ppm
$J_{PP} = 24$ Hz



$\delta = -13$ ppm $\delta = +26.4$ ppm
$J_{P-P} = 24$ Hz.

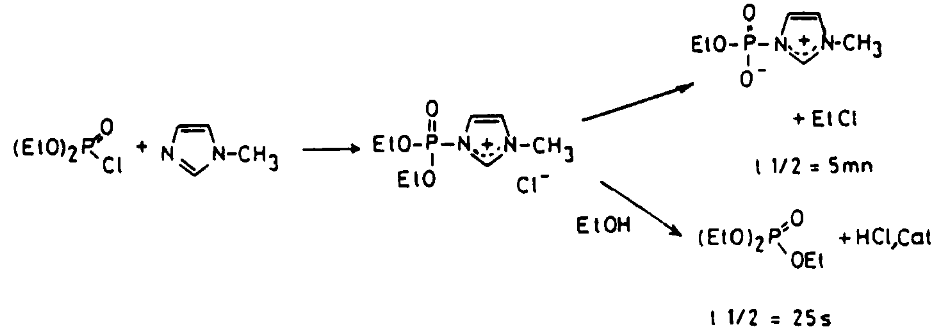
The complex formed between NmI and 2-chloro-1,3,2 dioxaphospholane also corresponds to a betaine.[23] The only case in which we have observed a different ionic species corresponds to the reaction of diethylchlorophosphate with NmI.



$\delta = 3.6$ ppm $\delta = -9.9$ ppm $\delta = -10.5$ ppm

The fast-formed product A ($\delta = -9.9$) disappears with time, while B ($\delta = -10.5$) increases all along the reaction process. We suppose that A corresponds to the initial exchange of NmI with Cl^-, and then Cl^- reacts at the carbon atom to form B and chloroethane.

Two points are essential: i) these betaines after they are formed (checked in the NMR tube) give no subsequent reaction with ethanol. On the other hand, in the coupling reaction of P—Cl compound with ethanol, plus NmI or HMPT, there is no signal corresponding to the betaines. ii) in the only case where we have been able to characterize an ionic intermediate, the half time of the decomposition process ($t_{1/2} = 5$ mn) is longer than the half time of the activated alcoholysis ($t_{1/2} = 25$ s).

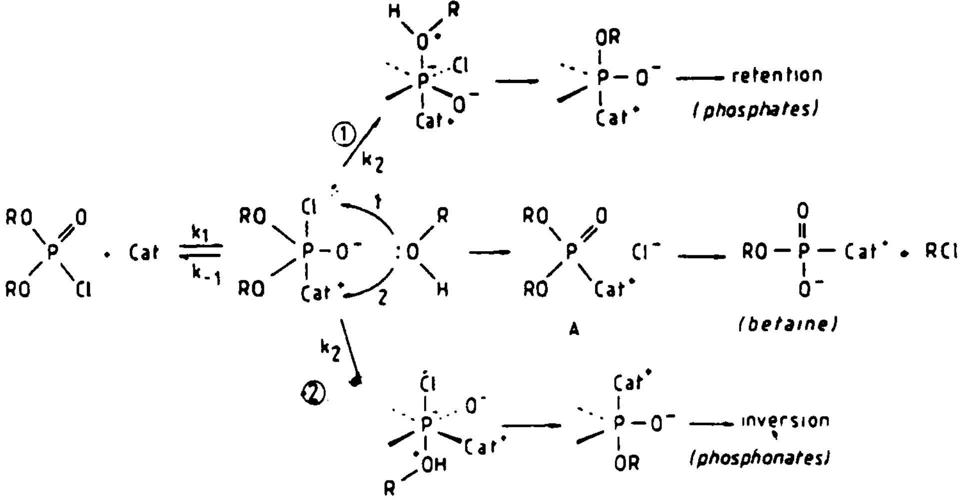


That means that decomposition of A to form betaine is a slow step. On the other hand, in the other cases, since we do not observe a species like A, the decomposition to form the betaine is a relatively fast step.

Therefore, we would expect the concurrent formation of betaine and phosphorus ester, especially in the case of HMPT, for which the complex order rate law implies that the reaction of A with alcohol is not a fast step and thus must compete with the decomposition of the intermediate.

The fact that concurrent formation of betaine is never observed by ^{31}P NMR is reliable evidence that A is not an intermediate in the activated alcoholysis.

The general mechanism we propose for the nucleophilic assisted substitution is the following:



The first step is the formation of a pentacoordinated intermediate in a reversible manner. If there is no nucleophile present in the medium, the P(5) species gives the ionic P(4) intermediate (which has been often postulated and sometimes characterized). This species is further changed to the more stable betaine.

If there is some nucleophile present, the P(5) species no longer accumulates in the medium, but quickly reacts with NuH to form the ultimate product.

Obviously the present conclusions which have been obtained in the case of chlorophosphorus derivatives would be also relevant to explain the chemical behavior of chlorosilanes. The important point to consider is that this mechanism is primarily concerned not with the hetero-atom but the involved reaction.

Finally, I would like to mention the analogy with the phosphoryl transfer reactions, catalyzed by enzymes. The overall stereochemistry has been considered as a tool to distinguish between the double displacement process, and the simple activation at phosphorus.[24]

Double Displacement—(2 INVERSIONS = 1 RETENTION)

$$\mathrm{E{-}XH} + \mathrm{A{-}}\textcircled{\scriptsize P} \rightleftharpoons \mathrm{E{-}X{-}}\textcircled{\scriptsize P} + \mathrm{AH}$$

$$\mathrm{E{-}X{-}}\textcircled{\scriptsize P} + \mathrm{BH} \rightleftharpoons \mathrm{B{-}}\textcircled{\scriptsize P} + \mathrm{E{-}XH}$$

Nucleophilic Assisted Displacement (1 INVERSION)

$$\mathrm{A{-}}\textcircled{\scriptsize P} + \cdot\mathrm{BH} \overset{E}{\rightleftharpoons} \textcircled{\scriptsize P}\mathrm{{-}B} + \mathrm{AH}$$

P. A. Frey (1982)

We have shown on simple models that different reaction conditions can affect the reactivity, but the stereochemistry is mainly governed by the nature of the phosphorus species. It would be of interest to consider the process of enzyme phosphoryl transfer catalysis in terms of pentacoordinated activated species.

ACKNOWLEDGMENTS

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