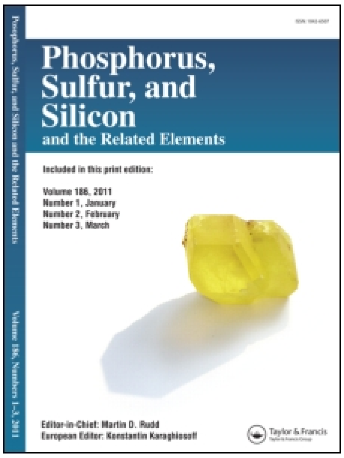

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NUCLEOPHILIC SUBSTITUTIONS AT SILICON AND PHOSPHORUS. A COMPARISON OF CONTROLLING FACTORS

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NUCLEOPHILIC SUBSTITUTIONS AT SILICON AND PHOSPHORUS. A COMPARISON OF CONTROLLING FACTORS

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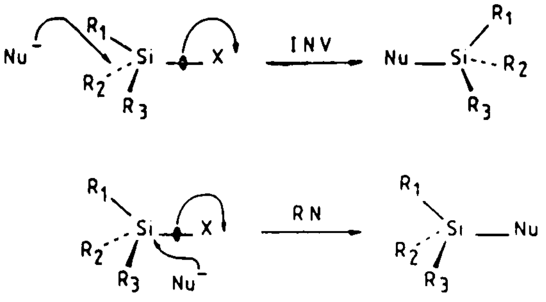
The stereochemical behavior of functional organosilanes is explained considering electronic factors. The reactivity depends on the stereochemistry. Retention and/or inversion are controlled by a frontier orbital process. The same conclusions can be extended to the mechanism of nucleophilic substitution of halogenophosphorus compounds. The kinetic data show that the electronic interaction between the incoming nucleophile and the leaving group is very deep when they are both in the apical position of a tbp intermediate. By contrast, the influence of the nucleophile is minimized when the approach of the nucleophile affords a 90° angle, i.e. overall retention at phosphorus.

The hydrolysis of silicates should be certainly more connected to the process of hydrolysis of phosphates through a mechanism involving pseudorotation of the pentacoordinated intermediates.

The nucleophilic substitution at silicon takes place with retention or inversion following the nature of the leaving group and following also the nature of the nucleophile. Stereochemical studies have been generally performed on monofunctional and also on some bifunctional compounds (cf. Figure 1).

The stereochemical studies concerning nucleophilic displacement in function of the nature of the leaving group have been performed by Sommer and other groups. The main results show that some leaving groups are displaced with inversion of configuration. This is the case of Cl, Br, OAc At the opposite OMe, H are displaced mainly with retention. F, SR are borderline cases which can be displaced either with retention or with inversion, following the nature of the nucleophile.

$$\mathrm{INV} \xrightarrow[\text{Cl, Br, OAc > F, SR > OMe, H}]{} \mathrm{RN}$$



The main controlling factors
—Nature of the leaving group
---Si—X
—Nature of the nucleophile

FIGURE 1

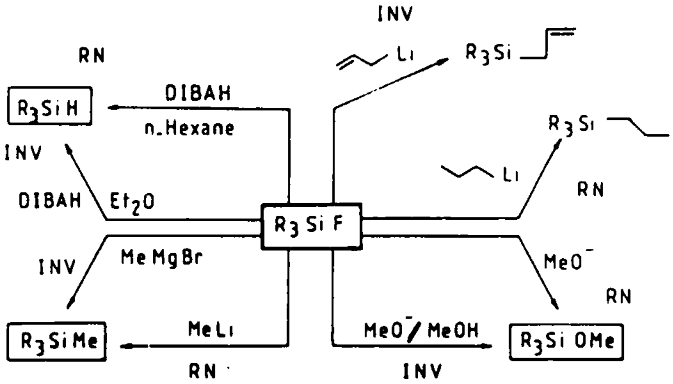


FIGURE 2

The nature of the nucleophile is very sensitive and some very simple changes can modify the stereochemistry of S_{N^2} of Si—F bonds as shown on Figure 2.

The case of *p*-substituted phenoxides is very illustrative. The *p*-nitro derivatives in which the negative charge is delocalized react with inversion. At the opposite extreme, the *p*-methoxy compounds, in which the charge is more concentrated, react with retention (cf. Figure 3).

Many other examples have been observed and reported as illustrated on Fig. 4.

All the experimental facts observed in the case of S_{N^2}(Si) can be explained using electronic factors and orbital considerations. Nguyen Trong Anh and C. Minot have presented a new proposal considering an extension of Salem's treatment for nucleophilic substitution at carbon. This extension considers that the S_{N^2}(Si) process is a frontier orbital process; the LUMO is the σ^* anti-bonding orbital of the Si—X bond. The HOMO is the high occupied molecular orbital of the nucleophile.

	Y =	M⁺ =	[α]D	
$1\text{-Np—}\overset{\text{Ph}}{\underset{\text{Me}}{\text{Si}}}\text{—SPh}$	MeO	Na^+	+6°	RN
	MeO	—*	+8°	RN
(+)	NO_2	Na^+	+3°	IN
	NO_2	—*	+8°	IN

*Reactions carried out with a cryptand specific for Na^+.

FIGURE 3

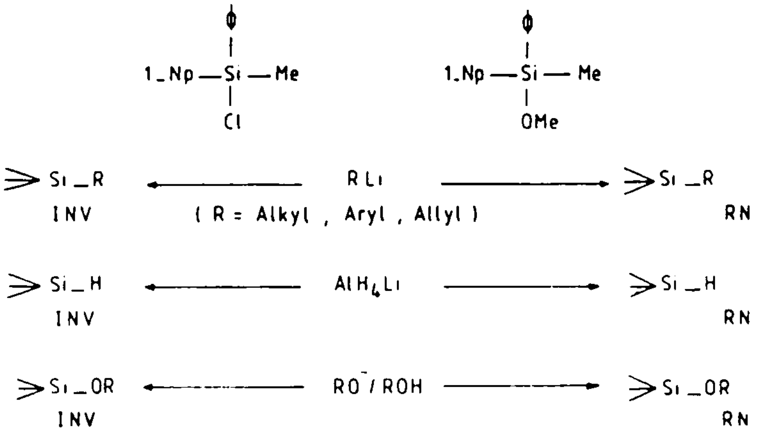


FIGURE 4

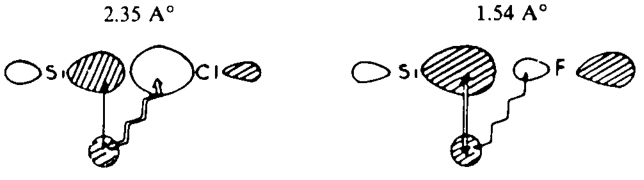
Figure 5 illustrates the proposal, and calculations have shown that in the σ^*, the big lobe is located inside of the Si—X bond. That means that the more favorable interaction between the LUMO and the HOMO takes place with this lobe corresponding to a front-side attack (retention).

However, it is necessary to take into account the out of phase overlap and also the electronic repulsion between the incoming nucleophile and the leaving group. When these parameters dominate, inversion of configuration is more favorable. If not, RN is the normal process.

We understand now more easily changes of stereochemistry with the nature of the nucleophile, the influence of the sizes of the lobe and the delocalization of the negative charge. When the charge is delocalized, the out of phase overlap increases and INV becomes the more favorable process.

It is very important to point out that at silicon, all the experimental facts can be explained considering electronic factors. Retention and/or inversion are controlled by a frontier orbital process. They are functions of the polarizability of the leaving group, the size of the lobes on the nucleophile and on the σ^* Si—X.

Each factor which affects one of those parameters changes the stereoselectivity of S_{N^2}(Si) processes.



The out of phase overlap is dominant

The In phase overlap is dominant

INV

RN

Ngyen Trong Anh and C. Minot

FIGURE 5

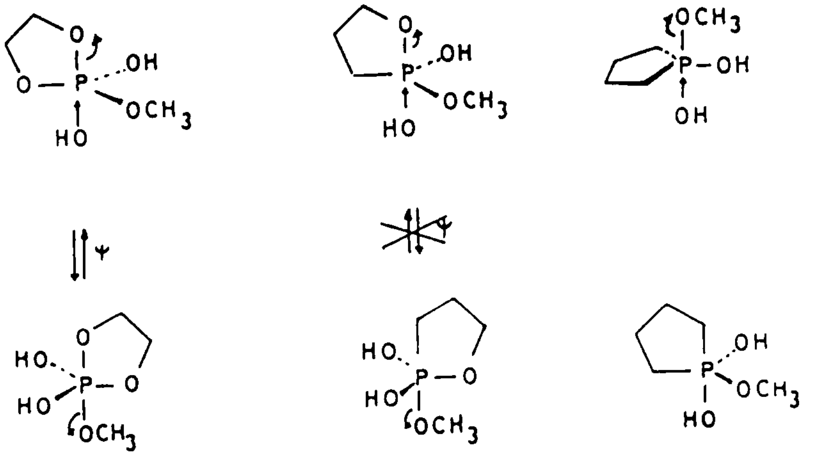


FIGURE 6

In contrast, in the case of phosphorus chemistry, the nucleophilic substitution on P(4) species is explained using the extension of Westheimer's concepts: the nucleophile is supposed to enter in apical position of the P(5) intermediate, and the leaving group is also considered to be displaced from an apical position. Pseudorotations are possible between intermediates as shown on Figure 6.

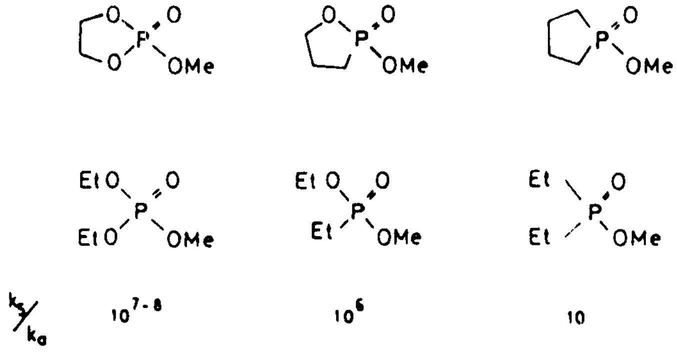
It is very important to remember that the origin of Westheimer's concepts comes from the studies of the hydrolysis of phosphates and phosphonates.

The main experimental fact is the great acceleration of five-membered ring derivatives (Figure 7).

The explanation which has been proposed by Westheimer is fully consistent with the data for the hydrolysis of phosphates and phosphonates.

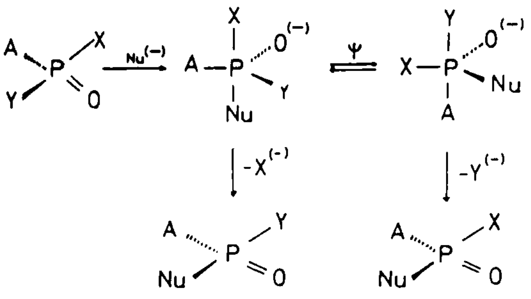
However, Westheimer's concepts have been later extended for explaining the nucleophilic substitution of P—X bonds (X = OR, SR, halogen). And the generally accepted scheme is shown on Figure 8.

Rate constants for hydrolysis



Westheimer (1968)

FIGURE 7



Inversion Retention

FIGURE 8

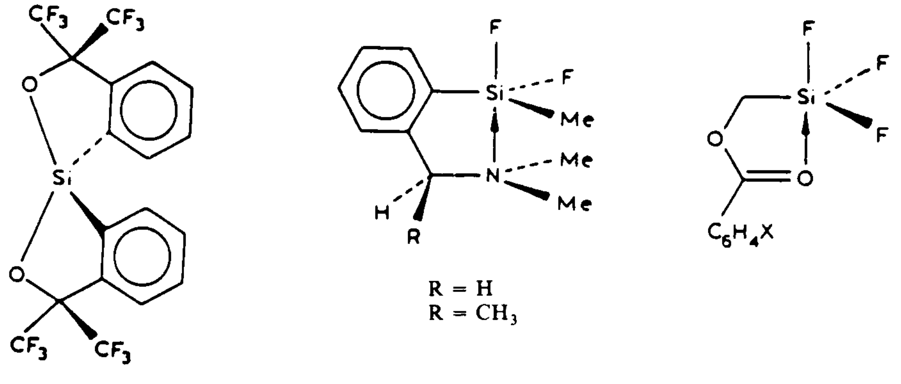
It is very surprising that the displacement at P and at Si are explained in so different ways: electronic factors in one case and in the other case structural factors connected to the apicophilicity of phosphoranes.

The first explanation for the apparent difference was to consider the possible lack of pseudorotation at silicon, since at phosphorus this process has been well studied in the case of many pentacoordinated phosphoranes.

The possibility of pseudorotation at silicon was not established until recently. J. C. Martin observed that in the case of siliconates and phosphoranes, the pseudorotation takes place with very similar energies. Meanwhile, we have reported evidence for pseudorotation at silicon in the case of molecules having an intramolecular coordination, of which the structure is a good model for nucleophile substitution, as shown in the Figure 9.

In conclusion, we can assert that pseudorotation is not the proper factor which can explain the difference in the commonly accepted rules for Si, P compounds.

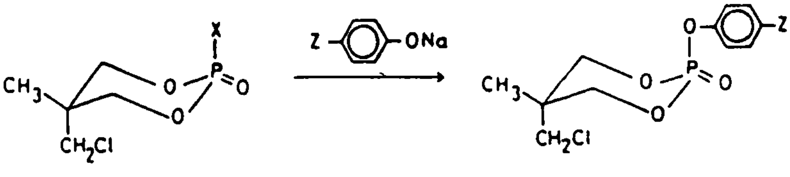
In order to develop a comparison between Si, P compounds, we have performed two kinds of experiments: i) We have studied the nucleophilic displacement of phosphorus-halogen bonds in order to compare their stereochemical behavior with



R = H
R = CH_3

J. C. Martin (1982) Corriu (1984) Voronkov (1980)

FIGURE 9



Z	%retention X = F	X = Cl	X = Br
MeO	100	72	65
Me	82	53	50
H	74	50	48
NO_2	50	12	(30)

FIGURE 10

Si—X bonds; ii) We have performed kinetic and stereochemical studies of the hydrolysis of cyclic alkoxysilanes, similar to the phosphates and phosphonates, earlier studied by Westheimer.

Concerning the first set of experiments, we have initially observed that the P—X bonds can also undergo two processes which are typical of Si, Ge compounds. The first one is the racemization of chiral derivatives with added nucleophiles; the second one is the nucleophilic activation to the nucleophilic substitution. These two processes were reported for the first time in the case of optically active chlorosilanes, and then extended to phosphorus compounds.

We have also studied the stereochemical behavior of P—X bonds in the reaction with *p*-substituted phenoxides. The results are shown on Figure 10.

It is interesting to point out the very great similarity between nucleophilic displacement at silicon and phosphorus. The P—F bond, like the Si—F bond is displaced with predominant retention, compared to P—Cl or Si—Cl bonds.

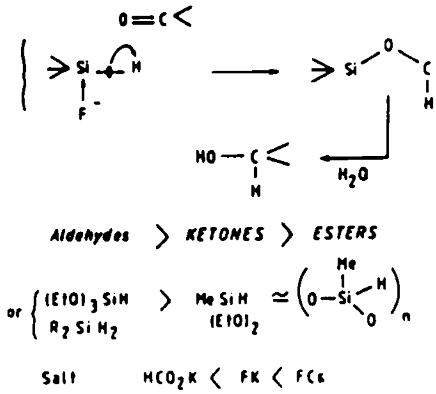
If we consider the influence of *p*-substituted phenoxides, we observe also a great parallelism between Si and P. The *p*-nitro derivative gives more inversion, the *p*-methoxy gives more retention. This stereochemical behavior could not be predicted using Westheimer's concepts. Since the fluorine is the more apicophilic group, in the case of fluorophosphanes, the inversion should be the more favorable process.

Another interesting feature to compare between silicon and phosphorus is the nucleophilic activation upon the nucleophilic substitution. In silicon chemistry, activation by $F^{(-)}$ is a well known process. The affinity of silicon for fluorine is so high that it is possible to activate Si—H, Si—Cl, Si—N by $F^{(-)}$ anions, either in homogeneous or in heterogeneous conditions.

The next Figure 11 shows a summary of the activation of Si—H bonds, giving a new selective way for the reduction of carbonyl groups.

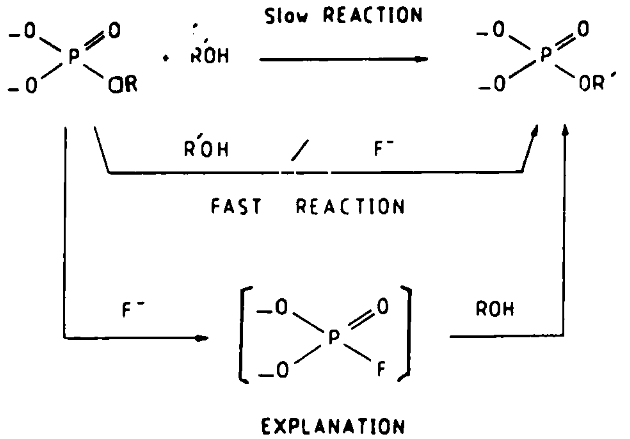
It is interesting to point out that this process is very typical of silicon chemistry. The same kind of activation has been observed in the case of phosphorus derivatives.

Ogilvie reported the substitution of phosphorus esters by alcohols, activated by $F^{(-)}$ anions. This author proposed the transient formation of P—F (4) intermediates, but these derivatives have been later shown not to be reactive with alcohols.



Heterogeneous condition with or without solvent

FIGURE 11



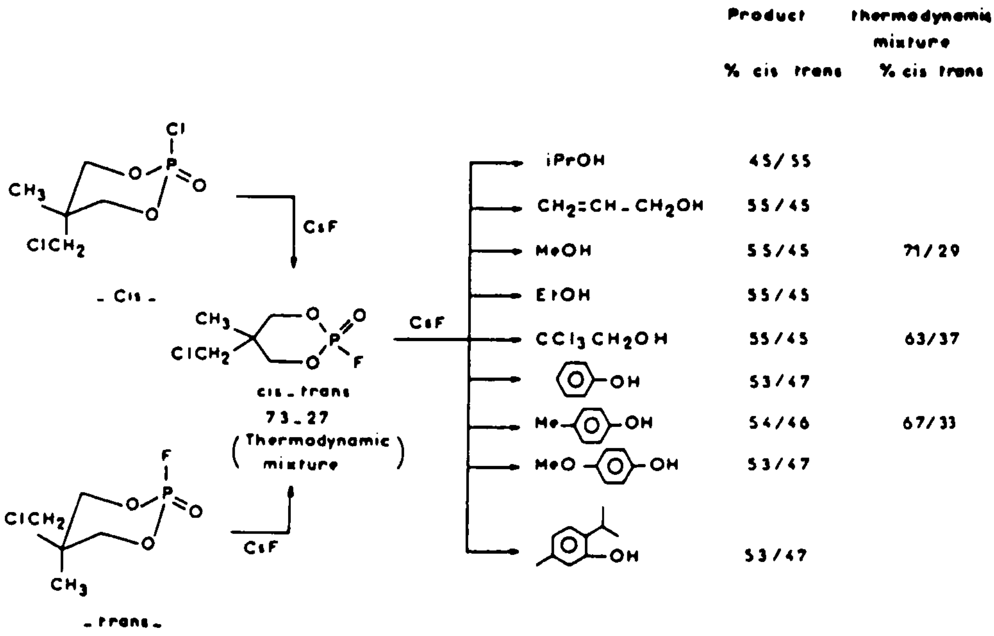
In fact, the reaction proceeds with an *excess* of $F^{(-)}$ anion, and we have shown from stereochemical data that the mechanism involves the transient formation of quasi-symmetrical "phosphoranoxide anion".

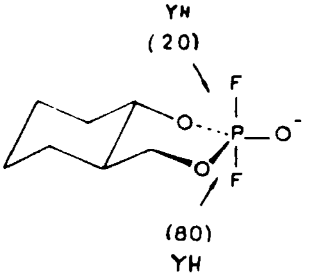
Our proposal is essentially based on the fact that whatever the isomeric ratio of the starting material, we always observe the same mixture of compounds. This ratio is independent of the alcohol concerned, and this is not a thermodynamic mixture.

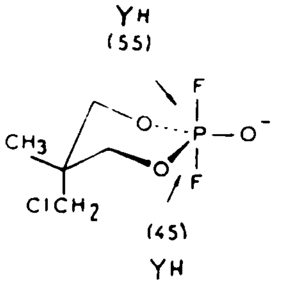
The most convenient explanation for these data is the formation of a quasi-symmetric intermediate, through the coordination of the fluorine anion to phosphorus. This intermediate undergoes the subsequent reaction with the alcohol, giving the phosphorus ester.

This process is obviously a nucleophilic activation to a nucleophilic substitution.

Now, I would like to report some results obtained in the case of alkoxysilanes, in order to compare with the phosphates described by Westheimer.

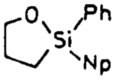
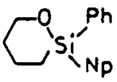
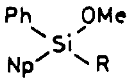
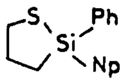
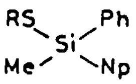






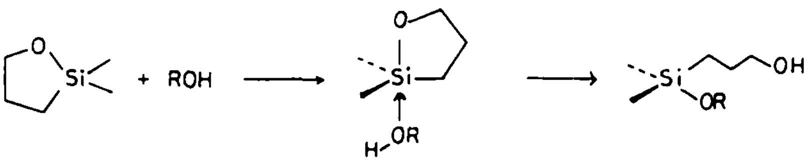
We have prepared optically active alkoxysilanes involved or not in a ring structure.

We have compared the reactivity of these compounds towards various nucleophiles like H_2O, MeOH or organometallics.

Nu	 1	 2	 5	 3	 6
H_2O	IN	IN	IN	—	—
MeOH	IN	IN	—	IN	IN
MeLi	RN	RN	RN	RN	RN
MeMgBr	RN	RN	RN	IN	IN

When the nucleophiles are not oxygenated compounds ($LiAlH_4$, RLi, RMgX), the stereochemistry is predominant retention, as expected for Si—O bonds, whatever the structure, acyclic or five-membered ring derivatives.

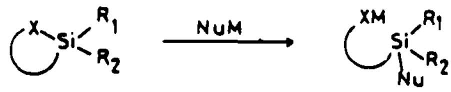
In contrast, in the case of hydrolysis or methanolysis, we note that the stereochemistry is inversion. Furthermore, the rate of the reaction is highly increased in the case of the five-membered ring compound with alcohols, but not with organometallics.

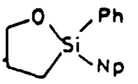
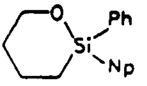


This fact is very surprising, but it can be compared to the results observed by Westheimer; and we can formulate now the following hypothesis: the change of stereochemistry, and the increase of the rate observed in the case of the five-membered ring compound, are connected with the symmetry of the intermediate. We must note that these facts are observed when an oxygen displaces another oxygen at silicon.

In the case of the hydrolysis of phosphates or phosphonates, such a geometry is always followed.

In order to check this hypothesis, we have studied the behavior of thio compounds. When the leaving group is not an oxygen but a sulfur, we have observed a great change in the reactivity. In the case of acyclic compounds, the Si—S bond is hydrolyzed faster than the Si—O bond, as expected. On the other hand, with the five-membered ring compound, the opposite occurs: the Si—O bond is hydrolyzed about 10^2 faster than the Si—S bond (cf Figure 17).



NuM	 1	 2	$t_{1/2}$ 2 / $t_{1/2}$ 1
H_2O (25°C)	60	$3 \cdot 10^5$	$5 \cdot 10^3$
MeOH (25°C)	30	$5 \cdot 10^5$	$1.6 \cdot 10^4$
MeLi (−78°C)	180	600	3.3
MeMgBr (20°C)	120	300	2.5

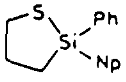
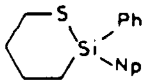
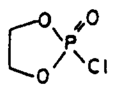
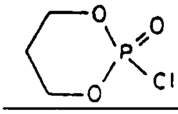
	 3	 4	$t_{1/2}$ 4 / $t_{1/2}$ 3
MeOH (15°C)	$3 \cdot 10^3$	10^5	33

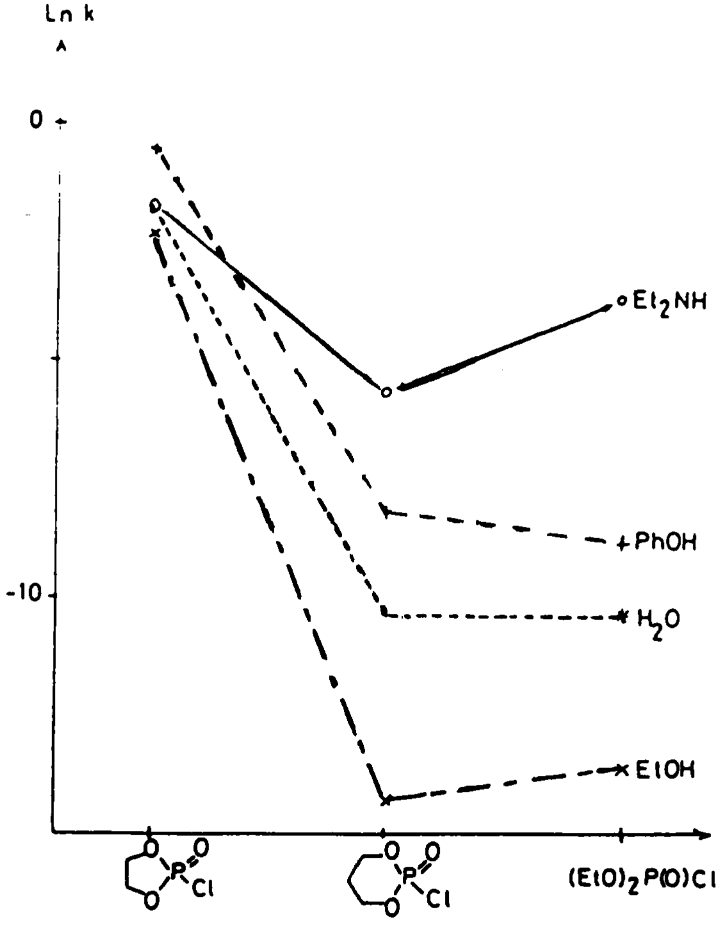
FIGURE 17

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.



These results illustrate the importance of an oxygen displacing another oxygen. The reactivity of carbon nucleophiles against Si—O bonds confirms our proposal.

They suggest that the hydrolysis of phosphates would be in fact, a particular case.

The explanation proposed by Westheimer accounts very well for the hydrolysis of phosphonates and phosphates, but we believe that it is not possible to extend such concepts to the general nucleophilic displacement of P—X bonds.

In order to test this assumption we have studied the nucleophilic substitution of highly reactive chlorophosphorus derivatives. In these compounds the general environment is close to this one of the models studied by Westheimer; the only difference is the chlorine atom instead of oxygen as leaving group.

The reactivity of these compounds with alcohols, water or amines corresponds to the only displacement of the P—Cl bond. We observe second order reactions (order one in chlorophosphorus derivative, order one in nucleophile).

The essential point to consider is that we do not observe the great acceleration observed by Westheimer in the case of five-membered ring phosphate, compared to the acyclic derivative. This ratio is now spread between 1 to 10^4 and depends on the nature of the nucleophile (cf Figure 21).

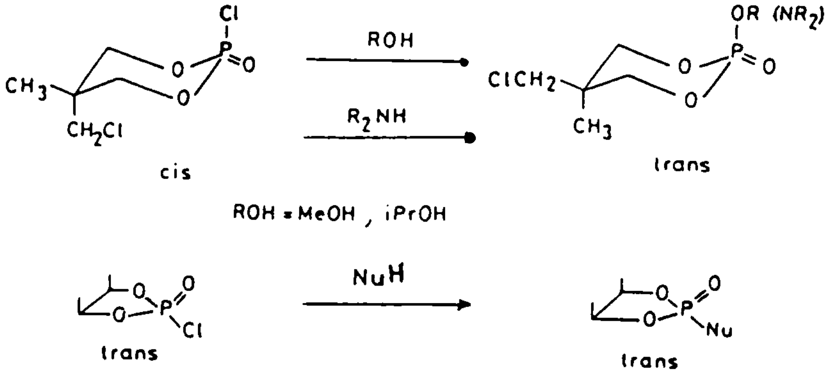
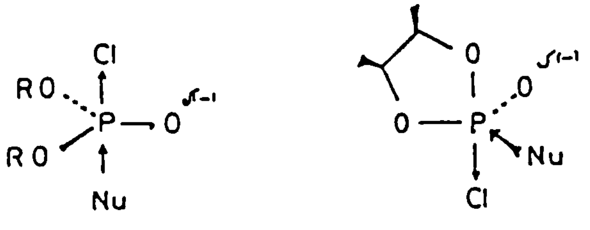


FIGURE 21

The reactivity is closely related to the stereochemistry of the nucleophilic displacement: with acyclic and six-membered ring compounds the predominent stereochemistry is inversion of configuration and we observe a very great influence of the nature of the nucleophile; the rate difference is between 1 to 10^5. At the opposite extreme, with the five-membered compound, which gives full retention of configuration, the influence of the nucleophile is very weak (between 1 to 8).

Such results cannot be accomodated with the concepts proposed by Westheimer. Furthermore the experimental results show that the electronic interaction between the incoming nucleophile and the leaving group is very important when they are both in apical position. By contrast, the influence of the nucleophile is minimized when the approach of the nucleophile affords a 90° angle $\widehat{XPNu}$, corresponding to retention of configuration (Figure 22).



Inversion (180°) Retention (90°)

FIGURE 22

The same remark has been already pointed out by us in the case of silicon compounds. (For a general discussion of Si stereochemical studies, refer to R. Corriu and C. Guerin, *Adv. Organometal. Chem.*, **20**, 268 (1982).)

In conclusion, we have shown that the nucleophilic substitution at phosphorus in the general case cannot be explained by the extension of Westheimer's concepts. These have been established in the case of highly symmetric reactions, in which an oxygen displaces another oxygen. As far as the general nucleophilic displacement is concerned, when the nucleophile is different than the leaving group, the mechanism is close to those proposed for the nucleophilic substitution at silicon.

We assume that the central atom is not the more important factor to consider: in fact, the general structure of the molecule and the nature of the nucleophile are the real determining factors, from a stereochemical point of view.

In other words, the S_{N^2} of P—F is, for example, similar to the S_{N^2} of Si—F bond.

On the other hand, the hydrolysis or the alcoholysis of silicates could be strongly connected to the hydrolysis of phosphates. Actually, we are performing some new experiments in order to confirm such an hypothesis.

Finally, I would like to thank my coworkers. Drs. Massé, Royo, Lanneau, Henner (Mr. and Mrs.) performed the earlier studies on functional silanes. Drs. Guérin carried out the work concerning the oxasilacycloalkanes and the detailed study of parameters controlling the stereochemistry. The general studies of phosphorus compounds are indebted to Drs. Lanneau, Leclercq. I have also to mention Drs. Dutheil and Fernandez.