

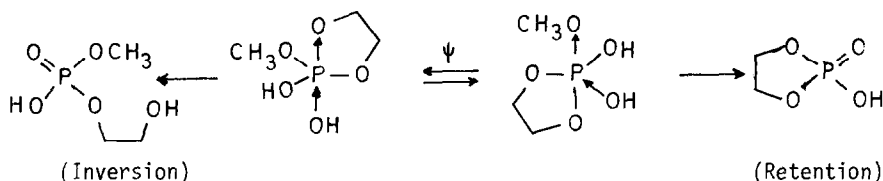
SILICON-PHOSPHORUS ANALOGIES
RATE CONTROLLING FACTORS IN $S_N2(P)$ REACTIONS
INFLUENCE OF THE NUCLEOPHILE FOR A GIVEN STEREOCHEMISTRY

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Abstract : $S_N2(P)$ reactions of chlorophosphates, which take place with inversion of configuration, are highly dependent upon the nature of the nucleophile. On the contrary, exocyclic substitutions of five-membered ring chlorophosphates with retention show a marked kinetic levelling effect.

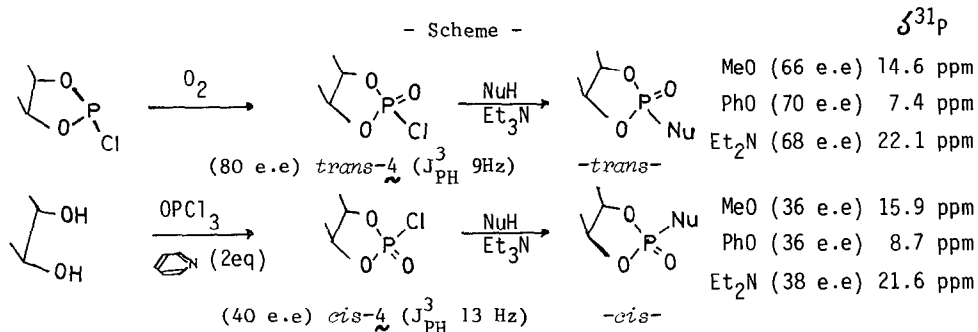
$S_N2(P)$ processes with displacement of the P-X bonds (X = halogen, OR, SR ...) are commonly accepted as an extension of Westheimer's concepts.¹⁻⁴ The current mechanism involves initial formation of the most stable P(5) intermediate of trigonal bipyramidal (tbp) geometry, with apical entry of the nucleophile. If the leaving group is also in apical position, the reaction proceeds directly (inversion). If the better leaving group is in equatorial position, ligand reorganization (via pseudorotation or other) allows consecutive departure from an apical position (retention).



The key finding of these interpretations is the large rate increase of the hydrolysis of ethylene phosphate derivatives relative to those of acyclic phosphates ($k_c/k_a = 10^{7-8}$ for both endocyclic and exocyclic cleavage in acidic conditions).⁵ However, most of these kinetic comparisons were concerned with phosphates and phosphonates, in which phosphorus is surrounded only by oxygen atoms, and in the case of hydrolysis reactions, involving the displacement of one oxygen by another one.^{1,6} In these cases, Westheimer's concepts, which had opened a new field of investigations in phosphorus chemistry, completely fit all the experiments, and very recently such ligand reorganizations have been evidenced.⁷ However, it is not "a priori" obvious that these concepts could be directly extended to all nucleophilic displacements at phosphorus of other nucleophiles and other leaving groups. For instance, Mislow had already pointed out the inapplicability of the principle of microscopic reversibility when the leaving group is not an oxygen. In such a case, apical entry or apical departure is no longer a rule, but other routes are theoretically possible.⁸

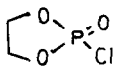
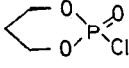
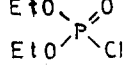
In the present paper, we have studied the kinetics and stereochemistry of nucleophilic displacement of the P-Cl bonds with different nucleophiles in the case of five-membered ring, 1, six-membered ring, 2, and acyclic, 3, chlorophosphates.

Nucleophilic substitutions of acyclic chlorophosphates proceed with inversion.⁹ In the case of six-membered ring compounds, the stereochemistry is much more dependent upon the nature of the nucleophile; however, inversion is predominant, even with phenols.¹⁰ The stereochemical behaviour of 4, 2-chloro-2-oxo-4,5 dimethyl-1,3,2-dioxaphospholane (scheme) allow us to conclude to predominant retention at phosphorus, in the case of five-membered ring compounds.¹¹⁻¹²



We have also carried out a detailed rate analysis of the reaction of 1,2,3 with various nucleophiles in strictly similar conditions. The reactions are of second-order (Table). The cyclic compound 1 is highly reactive. When we compare the influence of ring strain upon the rate of substitution, the ratios k_{c5}/k_{ac} vary considerably with the nature of the nucleophile.

Table : Second-order rate constants for the reactions of nucleophiles with P-Cl derivatives at 0°C in CH₂Cl₂

Nucleophile	 <u>1</u>	 <u>2</u>	 <u>3</u>	k_{c5}/k_{ac}
EtOH	1.1×10^{-2}	3.5×10^{-7}	1.2×10^{-6}	9×10^3
EtOH/Et ₃ N	11×10^{-2}	0.6×10^{-6}	1.2×10^{-6}	9×10^4
PhOH/Et ₃ N	68×10^{-2}	2.9×10^{-4}	1.6×10^{-4}	4×10^3
Et ₂ NH (2eq)	24×10^{-2}	-	3×10^{-2}	8
Et ₂ NH/Et ₃ N	21×10^{-2}	3.8×10^{-3}	2.8×10^{-2}	7.5
H ₂ O/Et ₃ N*	1.2×10^{-2}	-	3.5×10^{-5}	3.4×10^2

* Solvent CH₃CN

Westheimer noted a large rate increase in the exocyclic hydrolysis of methylethylene phosphate compared to the hydrolysis of trimethylphosphate ($k_5/k_a \approx 10^7$).⁵ A similar variation is not observed in the hydrolysis of chlorophosphates (k_5/k_a is only 3×10^2). Furthermore, diethylamine reacts at similar rates with 1, 3.

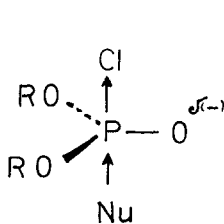
Two remarks are significant :

- in the case of 2, 3 which react with predominant inversion, the rate constants are highly dependent upon the nature of the nucleophile : amines are 10^4 more reactive than alcohols.

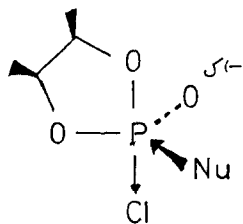
- in the case of strained 1, for which retention is noted at phosphorus, the rate constants are poorly dependent upon the nucleophile ($10^{-2} < k_2 < 7 \times 10^{-1}$).

These features are very different from those supporting Westheimer's concepts. But, they point out the importance of both the leaving group and the nucleophile, a situation well-documented in silicon chemistry.¹⁴

We have already mentioned silicon-phosphorus analogies, and $S_N2(P)$ of the P-F bonds with retention allowed us to propose an equatorial attack of the nucleophile to give the most stable tdp structure before departure of the leaving group.¹⁵ The same kind of argumentation may be invoked in the present case.



Inversion (180°)



Retention (90°)

The large influence of the nucleophile upon the rate of substitution with inversion is in good agreement with a $S_N2(P)$ mechanism involving apical entry and apical departure of the leaving group (synchronous or with transient formation of a tdp intermediate). The large kinetic effect we observed is as expected due to the mutual influence of apical ligands in the tdp species.¹⁶

On the contrary, in the equatorial attack, the nucleophile approaches the phosphorus species at 90° relative to the leaving group (retention). The levelling effect of the nucleophile corresponds to a situation in which the orthogonal nucleophile has only a small labilizing effect on the P-Cl bond. This assumption is in agreement with the theoretical calculation of the HOMO of pentacoordinate D_{3h} silicon intermediate, showing that orthogonal effects between equatorial attacking nucleophile and apical leaving group are very different from diapical interactions.¹⁷

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