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## Phosphorus, Sulfur, and Silicon and the Related Elements

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### Exocyclic Substitution of Five-Membered Ring Chlorophosphates: A Reexamination of the rule For Nucleophilic Substitution at Phosphorus

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EXOCYCLIC SUBSTITUTION OF FIVE-MEMBERED RING CHLOROPHOSPHATES  
A REEXAMINATION OF THE RULE  
FOR NUCLEOPHILIC SUBSTITUTION AT PHOSPHORUS

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**Abstract** Opposite to the  $S_N2(P)$  reactions taking place with inversion, which are highly dependent upon the nature of the nucleophile, exocyclic substitutions of five-membered ring chlorophosphates with retention show a marked kinetic levelling effect, emphasizing silicon-type argumentations.

$S_N2(P)$  reactions with inversion are generally supposed to involve the formation of trigonal bipyramidal (tbp) intermediates (or transition states) by attack of the nucleophile opposite to the leaving group. To explain retention at phosphorus it is customary to consider the initial formation of a tbp structure with the attacking nucleophile and the leaving group in apical-equatorial positions. Then, a 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 (or equatoriophilicity) of the different substituents.<sup>1-2</sup>

A completely different approach of this problem has been considered at silicon to explain the stereochemistry of  $S_N2(Si)$  reactions. Two predominant factors are essential: both, the stereoelectronic character of the nucleophile, and the nature of the leaving group govern the approach of the nucleophile.<sup>3</sup> Ab initio calculations are in good agreement with these interpretations.<sup>4</sup>

Obviously, the current mechanisms proposed in the two series, Si, P, are not reliable. Despite, we have already mentioned silicon-phosphorus analogies, and  $S_N2(P)$  cleavage of the P-F bonds with retention allowed us<sup>5</sup> to propose an equatorial attack of the nucleophile to give the most stable tbp structure before departure of the leaving group. Therefore, an important question was to know the origin of these different interpretations between Si and P compounds.

The mechanisms at phosphorus are commonly accepted as an extension of the Westheimer's concepts. But these concepts were considered in the case of phosphates and phosphonates, in which phosphorus

is only surrounded by oxygen atoms, and furthermore, in the case of hydrolysis reactions, involving the displacement of one oxygen by another one.<sup>1</sup> The experimental results were a large rate increase of the hydrolysis of ethylene phosphate derivatives relative to those of acyclic phosphates ( $10^7$ ) for both endocyclic and exocyclic cleavage in acidic conditions. In these cases, the Westheimer's concepts, which have opened a new field of investigations in phosphorus chemistry, completely fit all the experiments. Very recently such ligand reorganizations (via pseudorotation) have been evidenced by Knowles.<sup>6</sup>

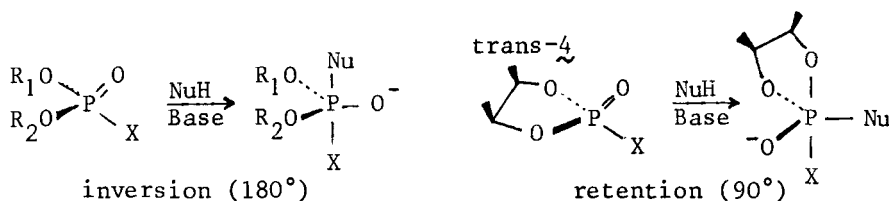
However, it is not "a priori" obvious that these concepts could be directly extended to all nucleophilic displacements at phosphorus. For instance, Mislow had already pointed out the inapplicability of the principle of microscopic reversibility when the leaving group is not an oxygen. In such a case, apical entry or apical departure is no more a rule, but other routes are theoretically possible.<sup>7</sup>

The first comparison we made concerned the endocyclic substitution of oxa (or thia)silacycloalcanes. Kinetic data showed a large rate increase ( $10^4$ ) for the methanolysis of the five-membered ring oxasilacyclopentane relative to the acyclic one (an oxygen replaces another oxygen). The same rate variation was not observed when the thio derivatives were substituted by alcohols (O replaces S) ( $4=10$ ).<sup>8</sup>

In the present communication,  $S_N2(P)$  reactions have been checked changing the nature of both the nucleophile and the leaving group. In order to compare more closely with Westheimer's data, based upon the hydrolysis of phosphates and phosphonates, we have studied the nucleophilic displacement of the P-Cl bond with different nucleophiles in the case of five-membered ring, 1, six-membered ring, 2, and acyclic, 3, chlorophosphates.

First of all, we have studied the stereochemistry of these reactions. Nucleophilic substitutions of acyclic chlorophosphates proceed with inversion.<sup>9</sup> 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 phenol.<sup>5-10</sup>

On the contrary, in the case of five-membered ring compounds, the stereochemical behaviour of 4, 2-chloro-2-oxo-4,5dimethyl-1,2,3-dioxaphospholane (scheme) allow us to conclude to predominant retention at phosphorus.<sup>11</sup> The two isomers of 4 were coupled respectively with methanol, phenol and diethylamine. The reactions are stereoselective. The attributions are made by comparison with the <sup>31</sup>P chemical shifts of the analogs, 4,5 dimethyl and 4,5 diphenyl-1,3,2-dioxaphospholanes-2-thiones.<sup>12</sup>

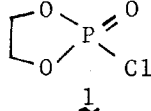
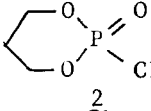
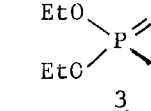


SCHEME

Secondly, we have carried out a detailed rate analysis of the reaction of 1, 2, 3 with various nucleophiles. The only characterized reaction is substitution of the P-Cl bond.<sup>13</sup> 1-3 obey a similar rate law with a representative serie of second order rate constants (Table). In the case of six-membered ring, 2, and acyclic compound, 3, constant values are highly dependent upon the nature of the nucleophile. Amines are much more reactive than alcohols ( $\Delta=10^4$ ). Such a difference is not observed in the case of strained 1. Very close rate constants are measured for various nucleophiles.

As a consequence, when we compare the influence of ring strain upon the rate of substitution, the ratios  $k_5/k_a$  considerably vary with the nature of the nucleophile. As a matter of fact, amines react at similar rates with five-membered ring and acyclic esters.

TABLE : Second-order rate constants for the reactions of nucleophiles with P-Cl derivatives at 0°C in CH<sub>2</sub>Cl<sub>2</sub>

Nucleophile				$k_5/k_a$
	<u>1</u>	<u>2</u>	<u>3</u>	
EtOH	$1.1 \times 10^{-2}$	$3.5 \times 10^{-7}$	$1.2 \times 10^{-6}$	$9 \times 10^3$
EtOH/Et <sub>3</sub> N	$11 \times 10^{-2}$	$0.6 \times 10^{-6}$	$1.2 \times 10^{-6}$	$9 \times 10^4$
PhOH/Et <sub>3</sub> N	$68 \times 10^{-2}$	$2.9 \times 10^{-4}$	$1.6 \times 10^{-4}$	$4 \times 10^{-3}$
Et <sub>2</sub> NH (2eq)	$24 \times 10^{-2}$	-	$3 \times 10^{-2}$	8
Et <sub>2</sub> NH/Et <sub>3</sub> N	$21 \times 10^{-2}$	$3.8 \times 10^{-3}$	$2.8 \times 10^{-2}$	7.5
H <sub>2</sub> O/Et <sub>3</sub> N*	$1.2 \times 10^{-2}$	-	$3.5 \times 10^{-5}$	$3.4 \times 10^2$

\* Solvent CH<sub>3</sub>CN

The situation is completely different to that observed in the case of phosphate ester hydrolysis, for which large kinetic effects were noted.

The great 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 *tbp* intermediate). The large kinetic effect is like it would be expected.<sup>14</sup> On the contrary, when the entering 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 little labilizing effect on the P-Cl bond.

Conclusions do not held phosphate-type argumentations. Therefore, direct extension of Westheimer's concepts for mechanistic purposes in the case of  $S_N2(P)$  reactions of P-X bonds is rather speculative.

Meanwhile, the present data are illustrative of the strong analogies found for nucleophilic displacement processes at Si and P. In the two series, we observe a high dependence of the rate upon the reactivity of the nucleophile for a given stereochemistry.<sup>15</sup> Also, we note a similar variation of the stereochemistry upon the structure around the heteroatom.<sup>3</sup> Further analogies will be held.

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