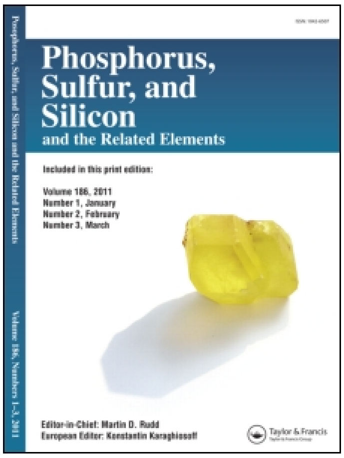

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MECHANISM OF NUCLEOPHILIC SUBSTITUTION AT TRICOVALENT PHOSPHORUS

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Abstract The mechanism of substitution reactions at tricovalent phosphorus, mainly the system $>$P-NR$_2$ + ROH, is discussed on the basis of stereochemistry, catalysis, kinetics and substituent effects.

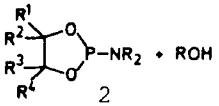
INTRODUCTION

Nucleophilic substitution reactions at tricovalent phosphorus (eq. 1) occur readily and are widely used for preparations of tricovalent phosphorus compounds; one recent application is the preparation of oligonucleotides by Letsinger's phosphite or Caruthers' phosphoramidite method.[1] For optimal results in these applications it is essential to know the factors which influence the substitution reactions; published information about these, however, is scarce. In order to obtain such information we have undertaken a study of the mechanism of substitution reactions at tricovalent phosphorus, and present here a summary of recent results from a study of simple model systems like 1 - 3.

$$>\text{P-L} + \text{Nu} \longrightarrow >\text{P-Nu} + \text{L} \qquad \begin{array}{l} \text{L} = \text{Cl, NR}_2\text{, OR, etc.} \\ \text{Nu} = \text{ROH, R}_2\text{NH, RLi, etc.} \end{array} \qquad \text{(eq. 1)}$$

$(Me_2N)_3P$ + Pr^iOH

1



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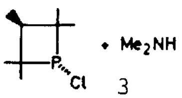


3

STEREOCHEMISTRY

In a number of cases we[2] and others[3] have found that the reactions proceed with inversion at phosphorus. Very clean inversion is observed when the nucleophile is a strong base like RLi or MeO$^-$ and the leaving group is OR, NR_2, or Ph. In other cases, e.g. 2, the products are initially formed with inversion, but they isomerize during the reactions.[2] Only when the leaving group is very good (Cl) are most reactions stereochemically unselective.

CATALYSIS

Reactions with NR_2 as leaving groups are catalyzed strongly by acids, e.g. $R_2NH_2{}^+Cl^-$. Carefully purified aminophosphines react very slowly with non-acidic ROH compounds, but since $R_2NH_2{}^+Cl^-$ is an impurity in most aminophosphine samples the reactions are usually found to be fast.

KINETICS

A few rate studies have been published on substitution of amino groups on trivalent phosphorus with alcohols or phenols.[4] However, since the rates have been measured without added catalysts they are probably not meaningful, because the rates are governed by the amount of acidic impurities. An example of this from our work is shown in Fig. 1 which shows typical rate curves for the system 1.

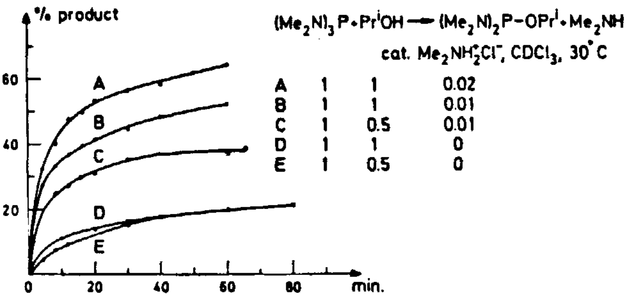
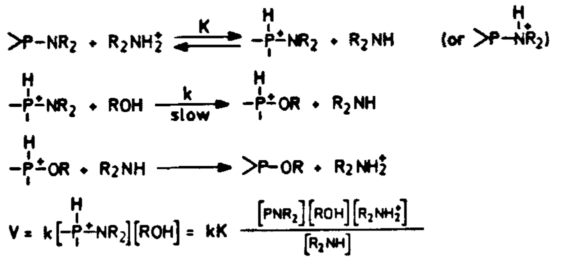


Fig. 1

In the absence of added catalyst (D and E) the rate is low and virtually independent of the nucleophile concentration, but when catalyst is added (A-C) the rates are roughly proportional to the nucleophile and the catalyst concentrations. Probably the catalytic step is rate limiting when no catalyst is added (D and E).

Rate constants have been calculated for several uncatalyzed systems by assuming second order rate expressions to apply in the early stages of the reactions.[4] Deviations from the second order behavior were ascribed to retarding effects from the accumulating R_2NH. We have studied several systems kinetically (concentrations measured by ^{31}P NMR integration) and found that the rate curves for catalyzed reactions can be simulated reasonably well by rate curves calculated from the expression shown (eq. 2). The expression is interpreted as the result of a two-step reaction (eq. 3). The

$$>P{-}NR_2 + ROH \xrightarrow{R_2NH_2^+X^-} >P{-}OR + R_2NH \qquad V = k_{obs}\,\frac{[PNR_2][ROH][R_2NH_2^+]}{[R_2NH]} \qquad \text{(eq. 2)}$$



$$>P{-}NR_2 + R_2NH_2^+ \underset{}{\overset{K}{\rightleftharpoons}} -\overset{H}{\underset{|}{P}}{}^{+}{-}NR_2 + R_2NH \qquad (\text{or } >P{-}\overset{H}{\overset{+}{N}}R_2)$$

$$-\overset{H}{\underset{|}{P}}{}^{+}{-}NR_2 + ROH \xrightarrow[\text{slow}]{k} -\overset{H}{\underset{|}{P}}{}^{+}{-}OR + R_2NH \qquad \text{(eq. 3)}$$

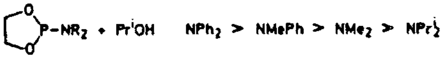
$$-\overset{H}{\underset{|}{P}}{}^{+}{-}OR + R_2NH \longrightarrow >P{-}OR + R_2NH_2^+$$

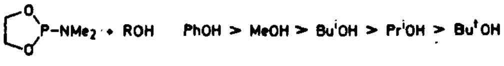
$$V = k[-\overset{H}{\underset{|}{P}}{}^{+}{-}NR_2][ROH] = kK\,\frac{[PNR_2][ROH][R_2NH_2^+]}{[R_2NH]}$$

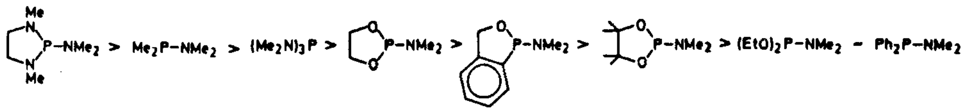
first step is the catalytic step, where phosphorus (or the leaving group) is activated for nucleophilic substitution. The second step is the proper substitution step. The product, of course, must loose a proton, either during the substitution step or in a fast third step.

SUBSTITUENT INFLUENCE ON THE RATE

According to (eq. 3), k_{obs} is a product of an equilibrium constant K and a rate constant k. A given change of substituents on P or N is expected to change K and k in opposite directions; electron donating substituents on P or N should increase K and decrease k, and vice versa for electron accepting substituents. The net result on k_{obs} is therefore difficult to predict. Relative orders of reactivity have been determined in a number of cases under identical conditions (1 M in reactants, 0.02 M in $Me_2NH_2^+Cl^-$, 40°C, $CDCl_3$):







The rate increase from NPr^i_2 to NPh_2 follows the leaving group ability and is opposite to the basicity; this indicates that the protonation site is P. Rate variations with nucleophile are as expected, apart from PhOH (self-catalysis). The variations with phosphorus substituents are less clear; apparently highly nucleophilic phosphorus compounds ($(R_2N)_3P$, Me_2PNMe_2) react fast because they have large K's, whereas other phosphorus compounds react more in accordance with their electrophilicity (controlled by k).

MECHANISM

A nucleophilic catalysis mechanism, proposed by Nifant'ev and Pudovik,[5] seems excluded because it would give products either with retention or racemization. A 4-center mechanism, advocated by Evdakov,[4] is unlikely also for stereochemical reasons, and should give a rate variation with NR_2 opposite to that found here. A mechanism as depicted (eq. 3) explains the catalysis and can accomodate the substituent effects. It does not, however, tell anything about the mechanism of the proper substitution step, apart from it being 1. order in nucleophile and prot. aminophosphine. The fact that the reactions normally proceed with inversion points to a S_N2(P) type mechanism, although inversion can be explained also by an addition-elimination mechanism. Probably the degree of bond making and bond breaking in the TS varies with the nucleophile, the leaving group and the substituents on phosphorus. The mechanism may approach the S_N1 limit for very good leaving groups like Cl, and there may be phosphorane or phosphoranide intermediates when these are stabilized by four- or five-membered rings, like those in **2** and **3**. However, neither phosphenium ions (S_N1 intermediates) nor phosphoranes (add.-elim. intermediates) have been observed during the reactions, although they can be made under slightly different conditions.

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