

# Physical Organic Perspectives on Phospho Group Transfer From Phosphates and Phosphinates

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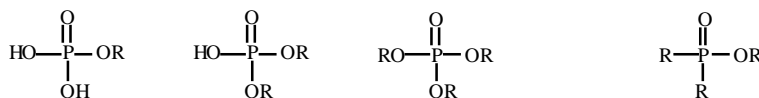
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**Abstract:** As phosphoryl transfer reactions are ubiquitous in biological chemistry, organic chemists have been very interested in the mechanisms of phosphate and phosphinate esters. Physical organic chemistry methods, including stereochemical studies, linear free energy relationships, and, most recently, heavy-atom kinetic isotope effects, have been used in the quest for mechanistic information about the chemistry of these compounds. This review summarizes what has been learned about the uncatalyzed phosphoryl transfer reactions of phosphate and phosphinate esters.

## 1. PHOSPHORYL TRANSFER FROM PHOSPHATE AND PHOSPHOROTHIOATE ESTERS

### INTRODUCTION

Phosphoric acid can be esterified at one, two, or three positions, yielding a monoester, a diester, or a triester, respectively (Figure 1). The structurally related phosphinates, discussed in part 2 of this review, have a single hydrolyzable ester group, and two alkyl groups bonded to phosphorus. Phosphate monoesters are ubiquitous in the biochemical world. Phosphorylated proteins are also phosphate monoesters, in which a serine, threonine, tyrosine or a histidine residue may be phosphorylated. In the latter case, where a phosphorus-nitrogen bond is present, the compound is termed a phosphoramidate rather than a phosphate ester. Aspartate residues are also sometimes phosphorylated, but usually as transient intermediates; such phosphoanhydrides are relatively reactive, in contrast to true phosphate monoesters, which are very stable compounds. The best known example of phosphodiester is probably the linkage connecting DNA and RNA. While there are no known naturally occurring phosphotriesters, such compounds comprise a number of pesticides and herbicides, which have found their way into the biological world though human intervention during the past half-century.



**Fig. (1).** At left, the structures of a phosphate monoester, diester, and triester, from left to right, respectively. At the far right, a phosphinate.

The importance of phosphate esters in nature has been one of the reasons for continued interest in the mechanisms of phosphoryl transfer that these compounds undergo. The mechanistic manifold is interesting in its own right, as phosphate esters have been shown to undergo phosphoryl transfer by a range of mechanisms depending primarily on

the alkylation state (mono-, di- or triester) of the reactant. This review will cover what is known of these mechanisms, summarizing historical results as well as more recent mechanistic studies.

### Mechanistic Summary

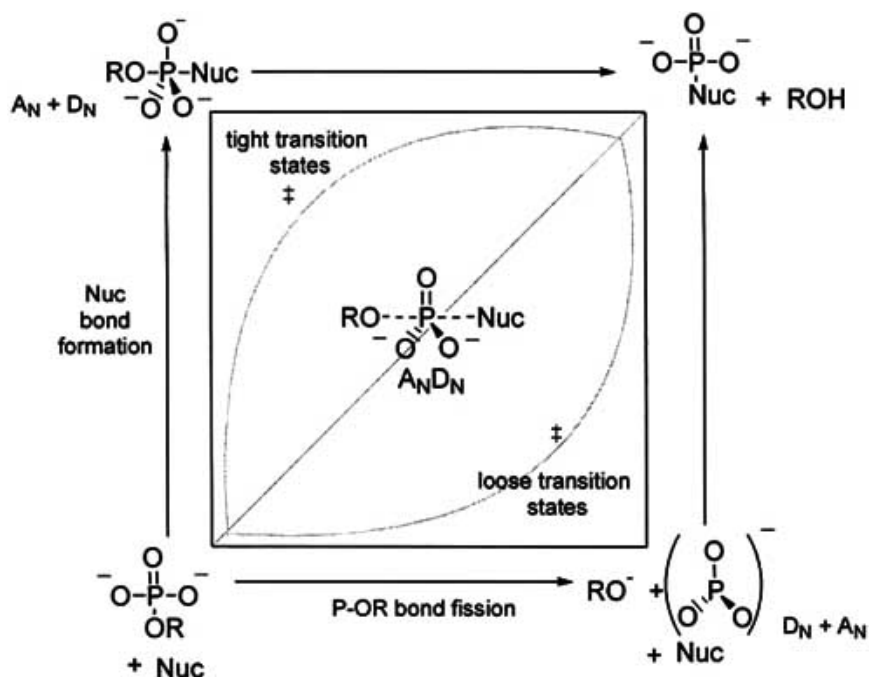
Phosphoryl transfer reactions can occur by three limiting mechanisms, shown graphically in the More-O'Ferrall-Jencks diagram [1].

One such limiting mechanism is a dissociative,  $S_N1$ -type two-step mechanism, designated  $D_N + A_N$  in the IUPAC nomenclature [2]. If a phosphate monoester reacts by this mechanism, a metaphosphate intermediate ( $PO_3^{-1}$ ) is formed, which is attacked by a nucleophile in a subsequent step. A second mechanistic possibility is an associative, addition-elimination mechanism ( $A_N + D_N$ ) in which a pentacoordinate phosphorane intermediate is formed in the first step, which expels the leaving group in a second step. Finally, a concerted mechanism ( $A_N D_N$ ) with no intermediate is also possible, and is in fact more common than either of the two other cases, as will be discussed below.

In the sections that follow, the mechanisms that have been delineated for the three classes of phosphate esters are

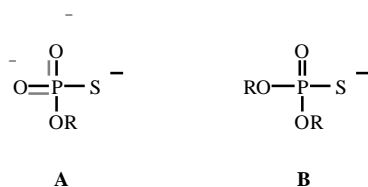
described. Analogs of these esters in which one of the nonbridging oxygen atoms of the phosphoryl group have been replaced by sulfur are referred to as phosphorothioates or as thiophosphates in the literature, and will also be discussed. This substitution has interesting consequences both on the distribution of charge in diesters and monoesters, as well as on the mechanisms of reaction. Experimental evidence indicates that for dianions of phosphorothioate monoesters, structure A in (Figure 3) is the most accurate representation of the charge distribution, with one negative charge localized on the sulfur atom and the other delocalized

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**Fig. (2).** In a More-O'Ferrall-Jencks diagram bond fission to the leaving group is shown along the horizontal axis, and bond formation to the nucleophile along the vertical axis. Stepwise mechanisms proceed along the lower right and upper left corners. Concerted mechanisms have transition states in the interior region of the diagram, depending on the relative synchronicity of leaving group departure and nucleophilic attack. A completely synchronous mechanism has a transition state along the diagonal through the center of the diagram. In this diagram a phosphate monoester reaction is shown, but the same potential mechanistic continuum applies to diesters and triesters.

between the two nonbridge oxygens [3]. In phosphorothioate diesters, experimental data is most consistent with a P-O bond order close to 2 and a negative charge on sulfur [4].



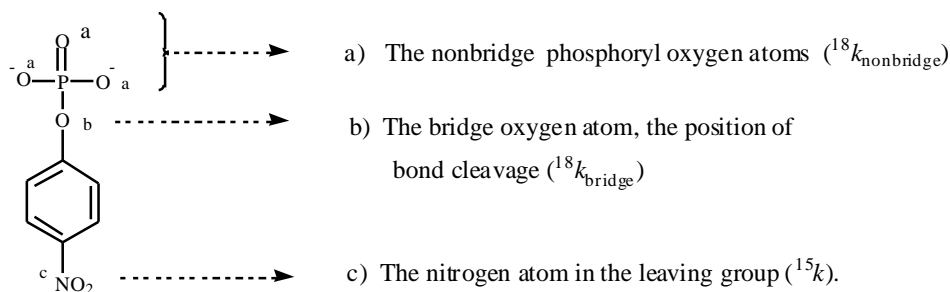
**Fig. (3).** Major resonance forms for the dianion form of a phosphorothioate monoester (A) and of a diester (B).

### Tools for Mechanistic Analysis

All of the classically used tools of physical organic chemistry have been used in the study of phosphoryl transfer. Linear free energy relationships [5] have been very

useful in delineating the degree of nucleophilic participation, and the extent of leaving group bond fission, in the transition states of these reactions. Solvent isotope effects, and, more recently, heavy-atom isotope effects [6] (Figure 4) have provided important additional information. Thermodynamic studies of the reactions yield values for the enthalpy and entropy of activation. While the interpretation of entropies of activation for reactions in structured solvents must be done with caution, such data show distinctions between reactions of the different classes of phosphate esters. In addition, the effect of pressure on the reaction rates allows the calculation of volumes of activation, which have been measured for a few phosphoryl transfer reactions.

The development of syntheses of phosphate monoesters which are chiral at phosphorus, and of methods for the stereochemical analysis of the reaction product, have allowed stereochemical studies of phosphoryl transfer to be



**Fig. (4).** A diagram of heavy-atom kinetic isotope effects showing the notation used to designate them, using *p*-nitrophenylphosphate as an example. The magnitude of  $^{18}k_{\text{nonbridge}}$  gives an indication of the degree of nucleophilic participation (looseness or tightness) of the transition state. The magnitude of  $^{18}k_{\text{bridge}}$  reflects the extent of P-O bond fission, and is affected if protonation of the leaving group occurs. When the leaving group is *p*-nitrophenolate,  $^{15}k$  reflects how much negative charge is delocalized into the aromatic ring.

carried out even for phosphate monoesters. These have been used to address the question of the intermediacy of metaphosphate in phosphoryl transfer reactions, and to test for the formation of phosphoenzyme intermediates in enzymatic reactions. Two synthetic methodologies for the preparation of phosphates made chiral by the use of the three stable oxygen isotopes were developed independently by Knowles and co-workers [7] and by Cullis and Lowe [8]. Substrates made chiral by the use of oxygen isotopes cannot be used for stereochemical studies of reactions that transfer the phosphoryl group to water, as there are only three stable oxygen isotopes, and the inorganic phosphate product has four equivalent oxygen atoms. Thus, studies of hydrolysis reactions have been done using phosphate ester reactants made chiral by the use of one sulfur atom and two oxygen isotopes, for example  $^{17}\text{O}$  and  $^{18}\text{O}$ , in the nonbridging positions. Phosphoryl transfer to water then yields a chiral thiophosphate product. Lowe and Cullis have described methods for the synthesis of chiral phosphorothioate monoesters [9,10]. Frey and Richard developed syntheses of chiral terminal phosphorothioate analogs of AMP, ADP and ATP [11].

### A. Monoesters

Depending upon the pH, phosphate monoesters exist as either the neutral, monoanionic, or dianionic species. The neutral species is present only under very acidic conditions, and reactions of this form have not been subjected to much study. With the exception of esters with highly activated leaving groups like 2,4-dinitrophenol, the monoanion species is much more reactive than the dianion [12].

### Reactions of Monoester Dianions

When the phosphoryl group is fully deprotonated the ester is in the dianion form, except for phosphorylated pyridines, which carry a formal net charge of -1. A large body of evidence indicates that these species, including acyl phosphates and phosphorylated pyridines [13], undergo phosphoryl transfer *via* a concerted process with a loose transition state, in the lower right region of the More-O'Ferrall-Jencks diagram (Figure 2). The supporting data includes near zero entropies of activation, small dependencies of rates on nucleophile basicity ( $\log k_{\text{nuc}}$ ), and large dependencies of rates on leaving group basicity ( $\log k_{\text{lg}} = -1.2$ ) [12]. The Brønsted results imply a large degree of bond fission to the leaving group, which is further supported by large bridge  $^{18}\text{O}$  kinetic isotope effects [14]. Despite very loose transition states, these reactions are not stepwise, and there is no evidence for the formation of free metaphosphate [13]. The collected evidence in favor of this mechanism has been reviewed [15]. When the phosphoryl group is made chiral using  $^{16}\text{O}$ ,  $^{17}\text{O}$ , and  $^{18}\text{O}$ , phosphoryl transfer occurs with inversion of configuration except in the very non-nucleophilic solvent and phosphoryl acceptor *tert*-butanol, where racemic *t*-butyl phosphate forms from chiral *p*-nitrophenyl phosphate [16,17]. This result implies that in *tert*-butanol a diffusible metaphosphate intermediate is formed in a two-step reaction. A mechanism can be postulated that explains this result without invoking metaphosphate [18] in which multiple nucleophilic attacks occur before proton loss from the initially-formed bridge-protonated *t*-butyl phosphate yields a stable product.

However, the entropy of activation of the reaction is significantly more positive (+24 eu)[19] than the aqueous hydrolysis (+3 eu)[20], suggesting that the mechanism has indeed become a 2-step  $\text{D}_{\text{N}} + \text{A}_{\text{N}}$  in which the first step is rate-limiting.

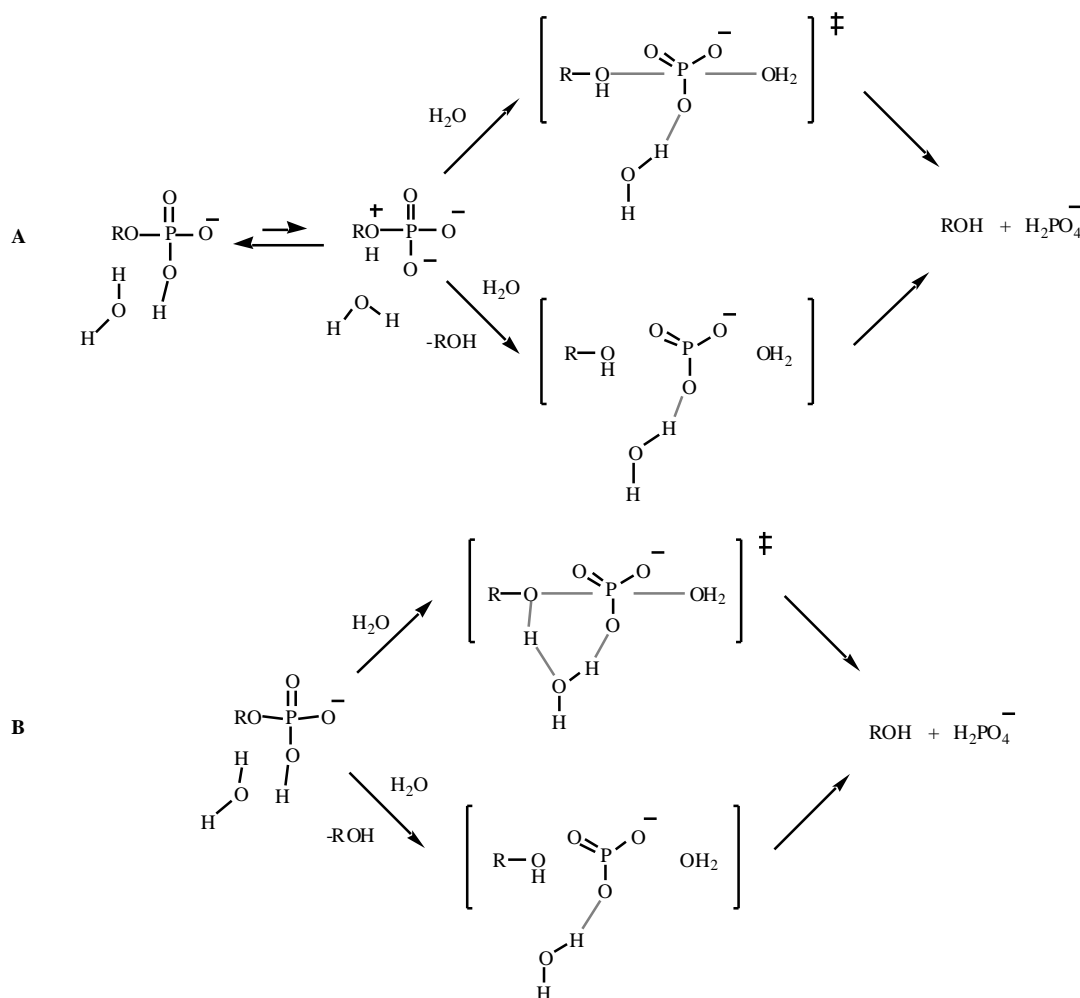
### Reactions of Monoester Monoanions

Linear free energy relationships with monoanionic phosphorylated pyridines indicate a loose transition state in which metaphosphate is not an intermediate [13]. As noted above however, these species, while formally monoanions, bear the phosphoryl group in the dianion form, and as such, are not good models for the reactions of what are generally referred to as monoanionic phosphate monoesters,  $\text{ROPO}_3\text{H}^{-1}$ . The hydrolysis of the monoanion of 2,4-dinitrophenyl phosphate is thought to be concerted [21], but the possibility of a metaphosphate intermediate has not been ruled out with esters having less activated leaving groups. A stereochemical study of the hydrolysis of phenyl phosphate monoanion indicates the reaction proceeds with inversion [16]. Such a result is consistent either with a concerted mechanism, or with a discrete metaphosphate intermediate in a preassociative mechanism.

A small  $\log k$  (-0.27) [12] for the hydrolysis of monoanions suggests that the leaving group is protonated in the transition state. There has been some debate over the timing of proton transfer and P-O bond fission. Kirby [12] postulated that protonation of the leaving group accompanies deprotonation of the phosphoryl group (probably *via* the intermediacy of one or more water molecules) and considered the timing of the proton transfer (Figure 5). He concluded that for less basic leaving groups, protonation occurs simultaneously with leaving group departure and is partially rate-limiting, while for more basic leaving groups, a bridge-protonated intermediate forms followed by rate-limiting P-O bond fission.

Consistent with this proposal, a solvent isotope effect ( $k_{\text{H}_2\text{O}}/k_{\text{D}_2\text{O}}$ , or  $^{\text{D}}k$ ) of 1.45 is found for hydrolysis of the monoanion of 2,4-dinitrophenyl phosphate at 39°C [12], while  $^{\text{D}}k$  for methyl phosphate monoanion is 0.87 at 100 °C [22]. Recent measurements reveal similar solvent isotope effects for the hydrolyses of the monoanions of *p*-nitrophenyl phosphate ( $0.96 \pm 0.01$ ) and *m*-nitrobenzyl phosphate ( $0.94 \pm 0.01$ ) [23]. In general, reaction mechanisms in which a proton is in flight in the transition state exhibit normal solvent deuterium isotope effects. This would suggest that the inverse values in the reactions cited above proceed by a mechanism in which proton transfer occurs in a pre-equilibrium step, prior to P-O bond fission. However, the solvent isotope effect itself is not sufficient evidence; the hydrolysis of ethyl orthocarbonate, despite being general-acid catalyzed [24], exhibits an inverse solvent isotope effect of 0.7 [25]. This was attributed a small primary deuterium isotope effect in a late transition state for proton transfer, counterbalanced by inverse fractionation factors.

The primary  $^{18}\text{O}$  kinetic isotope effect in the scissile P-O bond is significantly smaller, and in fact inverse, in the reaction of *m*-nitrobenzyl phosphate ( $0.9981 \pm 0.0002$ ) compared to the reaction of *p*-nitrophenyl phosphate ( $1.0087 \pm 0.0003$ ) [23]. This isotope effect is affected by protonation (which produces an inverse effect) and P-O bond fission (a



**Fig. (5).** Possible mechanisms for hydrolysis of monoanions of phosphate monoesters. In mechanism A proton transfer from the phosphoryl group (probably *via* the intermediacy of a water molecule) yields an anionic zwitterion intermediate. This may react in either concerted fashion (upper pathway) or *via* a discrete metaphosphate intermediate in a preassociative mechanism (bottom pathway). Mechanism B denotes proton transfer concerted with P-O bond fission. As with A, such a mechanism could either occur with concerted phosphoryl transfer to the nucleophile (upper pathway) or *via* a discrete metaphosphate intermediate in a preassociative mechanism (bottom pathway).

normal effect). The similar solvent isotope effect suggests a similar degree of proton transfer in both reactions, which would then lead to the conclusions that P-O fission is more advanced in the reaction of *p*-nitrophenyl phosphate. While this conclusion is at odds with what is expected on the basis of the Hammond Postulate, a possible explanation comes from calculations indicating that protonation of the P-O(R) ester oxygen atom weakens the bond to a greater degree when R=aryl than when R=alkyl [26].

### Phosphorothioate Monoesters

The hydrolysis reactions of O-aryl phosphorothioates (Figure 3A, R=aryl) using linear free-energy relationships found a value for  $\rho_{\text{lg}}$  of -1.1 [27] essentially identical to that for reactions of their phosphate ester counterparts. However, the stereochemical studies of phosphoryl transfer of chiral *p*-nitrophenyl [ $^{18}\text{O}$ ,  $^{16}\text{O}$ ]phosphorothioate show that ethanolysis [10,28] and hydrolysis [29] both proceed with a large degree of racemization, indicating the formation of free thiometaphosphate as an intermediate. The hydrolysis of the dianion

of 2,4-dinitrophenyl thiophosphate is accompanied by a significant positive volume of activation,  $+11 \text{ cm}^3 \text{ mol}^{-1}$  in contrast to the negative value ( $-4.8 \text{ cm}^3 \text{ mol}^{-1}$ ) measured with the corresponding phosphate ester [29]. This result also supports the notion that thiometaphosphate intermediates form in reactions of phosphorothioates in protic solvents, while phosphates under the same conditions react by a concerted mechanism.

The kinetic isotope effects in the leaving group in the reaction of the dianion of *p*-nitrophenyl phosphorothioate (*p*NPPT) are indicative of significant P-O bond fission and nearly a full negative charge on the leaving group in the transition state [30]. The KIEs are similar to those for hydrolysis of the *p*NPP dianion, indicating the transition states of both reactions are similar with respect to leaving group bond fission.

In reactions of the monoanions of phosphate and phosphorothioate monoesters, a proton is transferred from the phosphoryl group to the leaving group in the transition state (Figure 5). Protonation of *p*-nitrophenol results in an

inverse  $^{18}\text{O}$  isotope effect of 0.985 [31]. A transition state in which P-O bond cleavage and proton transfer are both far advanced would be expected to show an observed  $^{18}k_{\text{bridge}}$  that is approximately the product of 0.985 and the 1.0237 value for  $^{18}k_{\text{bridge}}$  observed for the dianion hydrolysis, which would be 1.008. The  $^{18}k_{\text{bridge}}$  for *p*NPPT monoanion hydrolysis of 1.0091, and that of 1.0087 for *p*NPP, are both close to this value. The magnitude of  $^{15}k$  is also significantly reduced relative to the dianion reaction, consistent with nearly full charge neutralization of the leaving group by protonation.

In summary, the transition states for the hydrolysis of phosphate and phosphorothioate monoesters are very similar to one another, with significant bond fission to the leaving group. The only significant difference is that the small degree of nucleophilic participation present in the reactions of phosphate monoesters is absent in reactions of phosphorothioate monoesters, the latter reacting by a fully dissociative,  $\text{D}_\text{N} + \text{A}_\text{N}$  mechanism.

## B. Diesters

The reactions of a wide range of nucleophiles with a series of aryl methyl phosphate diesters were found to show sensitivity to both the nucleophile and the leaving group [32]. The Brønsted  $\text{m}_{\text{nuc}}$  for attack by substituted pyridines on methyl 2,4-dinitrophenyl phosphate is 0.31, intermediate between that for attack by pyridines on the triester  $\text{ArOP}(\text{O})(\text{OCH}_3)_2$  and the monoester dianion  $\text{ArOPO}_3^{2-}$ , which are 0.61 and zero, respectively. The Brønsted  $\text{m}_{\text{nuc}}$  for attack by oxyanions is the same as for pyridines, 0.31 [33]. For attack by substituted pyridine nucleophiles on diesters of the form  $\text{ArOP}(\text{O})(\text{OCH}_3)\text{O}^-$ , the leaving group dependence,  $\text{lg}$ , ranges from -0.98 to -1.06. The  $\text{lg}$  for the alkaline hydrolysis is somewhat smaller, -0.64, in keeping with Hammond Postulate predictions that the stronger nucleophile should result in an earlier transition state. The observation of a significant dependence of the rate on both leaving group and nucleophile suggests a concerted mechanism. The most labile diester,  $\text{ArO}=2,4\text{-dinitrophenyl}$ , showed significant amounts of attack at aromatic carbon (nucleophilic aromatic substitution, with loss of methyl phosphate) in competition with attack at phosphorus, most notably with hydroxide and with primary amines. With less labile leaving groups, even *p*-nitrophenyl, attack at phosphorus seems to be the only pathway. An isotope labeling study of the alkaline hydrolysis of ethyl 4-nitrophenyl phosphate indicated only P-O fission occurs even at  $1\text{N } [\text{OH}^-]$  [34].

Kinetic isotope effects are also indicative of a concerted mechanism for these diesters. The  $^{18}k_{\text{bridge}}$  KIE in the oxygen atom of the scissile P-O ester bond in several diesters of the type *p*-nitrophenyl- $\text{OP}(\text{O})(\text{OR})\text{O}^-$ , where R has been alkyl or aryl, are  $\sim 0.5\%$  normal, indicative of bond fission in the transition state. These values are much smaller than those observed in reactions of the monoester *p*-nitrophenyl- $\text{OPO}_3^{2-}$ , which mirrors the comparative Brønsted  $\text{lg}$  values for diesters compared with monoesters. An observed nucleophile  $^{18}\text{O}$  isotope effect of 6.8% ( $1.068 \pm 0.007$ ) was measured for the attack of hydroxide on the diester thymidine-5'-*p*-nitrophenylphosphate [35]. This observed isotope effect consists of an equilibrium isotope effect of 1.040 for the deprotonation of water, and a 1.027 KIE for nucleophilic attack. The large normal KIE is evidence for

direct attack by hydroxide in the rate-limiting step, and together with the presence of a normal  $^{18}\text{O}$  KIE in the scissile oxygen atom, points to a concerted mechanism.

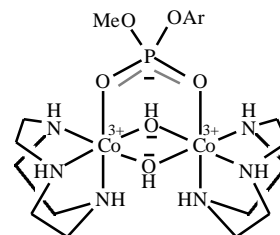
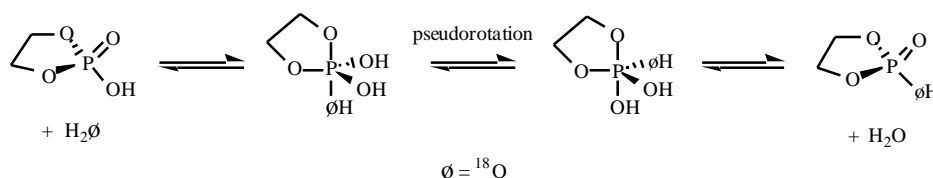


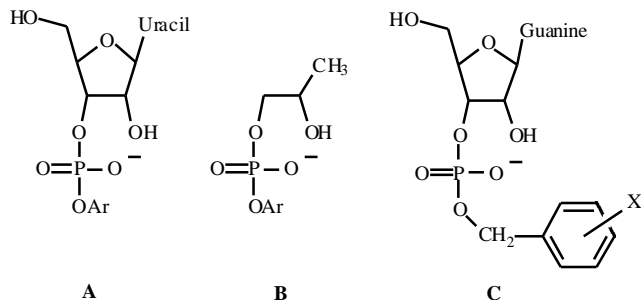
Fig. (6).

Studies of methyl aryl phosphodiester coordinated to a dinuclear  $\text{Co}(\text{III})$  complex (Figure 6) show that coordination results in significantly faster rates of hydrolysis; the methyl *p*-nitrophenyl phosphate complex undergoes hydrolysis about  $10^{11}$  times faster than the corresponding uncomplexed diester [36,37]. pH-rate studies support a specific base mechanism, in which the nucleophile is a deprotonated bridging oxide [36]. The  $\text{lg}$  of -1.38 for reactions of the coordinated diesters is much larger than for the alkaline hydrolysis of uncoordinated phosphodiester ( $\text{lg} = -0.64$ ). The data suggest that leaving group bond fission in the hydrolysis of the complexed diester is about twice as advanced in the transition state as for the hydrolysis of the uncomplexed diester [36]. Kinetic isotope effects with the *p*-nitrophenyl ester show that this rate acceleration is accompanied by a change in mechanism compared to uncomplexed phosphate diesters [38]. KIEs in the leaving group (both  $^{18}k_{\text{bridge}}$  and  $^{15}k$ ) indicate much greater P-O bond fission and more negative charge on the leaving group in the transition state of the hydrolysis of complexed methyl *p*-nitrophenyl phosphate than in the hydrolysis of uncomplexed alkyl-*p*-nitrophenyl phosphodiester, consistent with the larger  $\text{lg}$ . Most telling is a large inverse nucleophile,  $^{18}\text{O}$  KIE of  $0.937 \pm 0.002$ . While no large experimental inverse nucleophile KIEs are known, large inverse EIEs are common. Thus, this value is most consistent with a mechanism in which the bond to the nucleophile has been fully formed before the rate-determining transition state [38]. These results are best accommodated by a stepwise mechanism, in which nucleophilic attack occurs to form a coordinated phosphorane intermediate, followed by rate-limiting expulsion of the leaving group. In this mechanism the observed nucleophile isotope effect is an equilibrium isotope effect between the reactant shown in (Figure 6), and the phosphorane intermediate [38]. In the transition state of the rate-limiting step, the P-O bond is substantially broken and there is a substantial negative charge on the departing nitrophenolate.

Diester, as well as triesters, can have cyclic structures if two of the ester groups are joined. Cyclic phosphodiester incorporating five-membered rings are much more reactive than either their acyclic counterparts, or diesters with larger rings. It was believed that the enhanced reactivity resulted from ring strain in the reactant that was alleviated in the phosphorane-like transition state [39]. More recently, differences in solvation have been proposed to account for the rate enhancement [40].



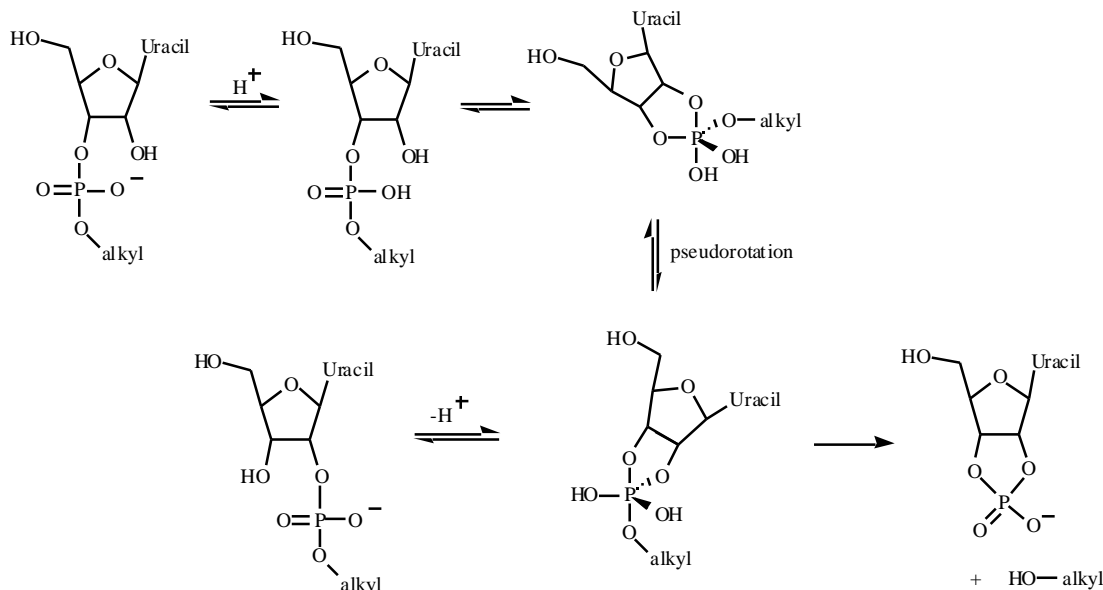
**Fig. (7).** Mechanism by which  ${}^{18}\text{O}$  from water can exchange into ethylene phosphate.



**Fig. (8).** Models for RNA.

The possibility of  ${}^{18}\text{O}$  exchange with labeled water during the hydrolyses of the cyclic diester ethylene phosphate (Figure 7) has been used to examine the question of whether phosphorane intermediates reversibly form, or whether such species are transition states. For exchange to occur, a phosphorane must form with a sufficient lifetime to allow pseudorotation to occur (Figure 7). Oxygen exchange occurs during acid hydrolysis, but not under alkaline conditions [41]. Similar findings came from a study of the isomerization of glycerol-2-monophosphate to 1'-monophosphate in  ${}^{18}\text{O}$ -water. Incorporation of  ${}^{18}\text{O}$  from water accompanies the reaction under acidic conditions, but not under basic conditions [42]. These results, and others, (see [43] and references therein) suggest that protonation is necessary for phosphoranes to exist as stable species (i.e., intermediates) during phosphoryl transfer reactions, and are transition states under conditions where they are dianionic.

Because of the biological significance of RNA and interest in the mechanism of ribonuclease, which catalyzes the cleavage of RNA, considerable study has been devoted to the reactions of dinucleotides and similar molecules like those in (Figure 8). The  $\rho_{\text{lg}}$  values were measured for the cyclization under alkaline conditions to form the 2', 3' cyclic phosphate of a series of aryl esters 8A, giving an estimate of the negative charge on the aryl oxygen atoms in the transition state.  $\rho_{\text{lg}}$  values of -0.59 and -0.54 were found for the imidazole-catalyzed general base, and for the hydroxide specific base reactions, respectively [44]. These are very similar to the  $\rho_{\text{lg}}$  of -0.56 for the hydrolysis of 8B measured by Usher [45]. For the general base-catalyzed reaction of 8A, the dependency of rate on base strength yielded a Brønsted slope of +0.67. These data indicate that the general base acquires a charge of  $\sim +0.67$  in the transition state, while normalization of  $\rho_{\text{lg}}$  using the  $\rho_{\text{eq}}$  of 1.74 for the net reaction yields a Leffler index [46] of 0.34, indicating that only about a third of a negative charge is transmitted to the leaving group [44]. The rest of the negative charge resides either on the 2'-hydroxyl or the phosphoryl group. These data were taken as evidence for a concerted mechanism with a phosphorane-like transition state [44]. The  $\rho_{\text{lg}}$  value is -0.9 for the alkaline cyclization of 8C [47], yielding Leffler index of 0.5, compared to 0.34 for 8A. Similarly, the alkaline cyclization of series of uridine-3'-alkylphosphates yields a  $\rho_{\text{lg}}$  value of -1.28 [48]. These results are consistent with expectations from the poorer alkyl leaving groups of a later transition state in a concerted reaction.



**Fig. (9).** Acid-catalyzed isomerization and cyclization. Proton transfers involved in formation of the phosphorane intermediate are assisted by solvent water.

The kinetics for the phosphoryl cleavage and migration reactions of dinucleotide-3'-phosphate diesters and related compounds have been studied, most recently by Lonnberg and co-workers [49]. Under acidic conditions, alkyl-phosphate migration (to form a 2'-phosphate diester) and cyclization (to a cyclic 2',3' phosphate) (Figure 9) proceed at comparable rates, *via* a common intermediate. Under very acidic conditions the mechanism involves a protonated (cationic) phosphate ester, and at lower acid concentrations, by attack on the neutral phosphodiester. Near neutral pH, a pH-independent isomerization of the diester is the major reaction, while under alkaline conditions, hydrolysis of the phosphodiester bond is the only reaction observed [49]. More recently the  $^{18}\text{O}$  kinetic isotope effects were measured for the isomerization and cleavage reactions of uridine 3'-*m*-nitrobenzyl phosphate [50]. At pH 2.5, an inverse  $^{18}k_{\text{nonbridge}}$  KIE 0.9904 for the cleavage reaction is consistent with protonation of the phosphoryl group to form a neutral phosphorane intermediate. The  $^{18}k_{\text{nonbridge}}$  and  $^{18}k_{\text{bridge}}$  KIEs of unity for the pH-independent isomerization at neutral pH

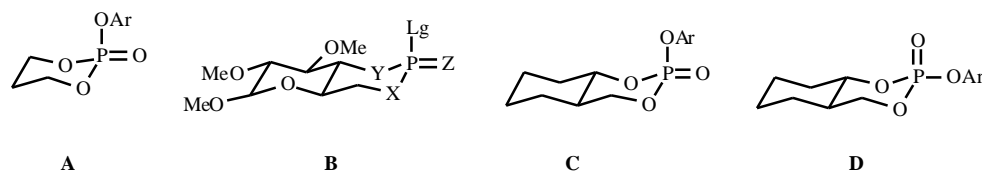


Fig. (10). In B, the leaving group is denoted by Lg, Z was oxygen or sulfur. X and Y were oxygen, sulfur, or N-methyl.

support a stepwise mechanism with a monoanionic phosphorane intermediate. The observation that in anhydrous *tert*-butanol the isomerization does not take place demonstrates the requirement for a water-mediated proton transfer for formation of the phosphorane intermediate. Finally, the  $^{18}\text{O}_{\text{bridge}}$  KIE of 1.0272 for the cleavage reaction at pH 10.5 is consistent with a concerted reaction in which the leaving group departs with a substantial negative charge. This is also consistent with the notion that a dianionic phosphorane is viable as a transition state but not an intermediate [43].

Phosphorothioate analogs of phosphodiesters undergo hydrolysis more slowly than their monoester counterparts, in contrast to the trend in relative rates for monoesters. The rates of reaction of methyl 2,4-dinitrophenyl phosphate/phosphorothioate with a variety of nucleophiles give "thio effects" ( $k_{\text{O}}/k_{\text{S}}$ ) in the range of 4 to 11 [51]. In contrast, thio substitution has no effect on the rate of alkaline hydrolysis of RNA [52].

Linear free energy relationships have been examined for the base-catalyzed intramolecular cyclization of uridine 3'-(aryl phosphorothioate)s, (analogous of 8A in which a nonbridging oxygen of the phosphodiester is replaced by sulfur) to determine the dependence of the reaction on the basicity of the leaving group, as well as on the basicity of the catalyst [53]. These compounds are the thio analogs of those studied by Williams and co-workers (Figure 8A). The reaction rates of the phosphorothioates are from 1.2 to 3.6-fold slower than the corresponding phosphates. The Brønsted  $\lg$  values for the imidazole and the hydroxide-catalyzed reactions of the phosphorothioate esters are -0.63 and -0.55, respectively, very similar to the values of -0.59 and -0.54 of

the phosphate ester reactions. The Leffler values of 0.59 for deprotonation by the base, and 0.36 for P-O bond fission do not balance, and are also similar to the values of 0.67 and 0.34 found for the phospho analogs. Likewise, this indicates negative charge buildup on the central group of atoms (the phosphoryl group and the attacking oxygen) [53]. Collectively, the data reveal that there is no significant mechanistic difference between reactions of phosphodiesters and their phosphorothioate counterparts.

### C. Triesters

As neutral compounds, triesters do not repel nucleophiles like their anionic diester and monoester counterparts. Thus, phosphotriesters are the most reactive of the three classes of phosphate ester. Kirby obtained linear free energy relationships for the dependence of rate on both nucleophile and leaving group for a series of 6-membered ring cyclic triesters (Figure 10A) [33]. Such esters react at comparable rates to their acyclic counterparts, in contrast to 5-membered cyclic phosphate esters, which react at much faster rates.

The LFER results showed that the dependency of the rate on the leaving group ( $\lg$ ) was smallest with the most basic oxyanion nucleophiles (such as hydroxide, for which  $\lg = -0.4$ ) and increased as the basicity of the nucleophile decreased (for acetate,  $\lg = -0.88$ ). This, and other observations, were interpreted to favor, though not require, a two-step mechanism involving a pentacoordinate phosphorane intermediate [33].

Subsequent stereochemical studies of related compounds (Figure 10B) with a wide variety of nucleophiles and leaving groups show that whether the transfer reaction occurs with retention or inversion of configuration depends not only on the nucleophile and leaving group, but also the solvent, counterions present in the reaction solution, and other heteroatoms in the 6-membered ring [54]. The latter effect is shown in the contrast between the displacement of *p*-nitrophenoxide by ethoxide, which proceeds by 88% retention when X=O (Figure 10B where Y, Z = O, Lg=*p*-nitrophenyl), but 68% inversion when X=N-CH<sub>3</sub> [54]. Studies with analogs of 10B, with both axial or equatorial orientation of Z and Lg, revealed that the stereochemical outcome is independent of the initial axial or equatorial orientation of the leaving group.

In the reactions described above, retention can only be accommodated by formation of a phosphorane intermediate, followed by pseudorotation before loss of the leaving group. Inversion could result either from a concerted reaction, or by a stepwise process if the phosphorane collapses before pseudorotation can occur. The stereochemical and LFER data indicate that a continuum of both mechanisms exists. In a study of similar cyclic triesters (Figure 10C and D) that combined LFER studies, stereochemical analysis, and

solvent isotope effects, Gorenstein found a similar trend in  $\lg$  values as a function of attacking nucleophile. These and the stereochemical data are strong evidence for a mechanistic continuum from concerted to stepwise reactions of 6-membered cyclic phosphate triesters [55].

LFER data support a concerted reaction with no intermediate in reactions of acyclic phosphotriesters with aryl leaving groups, as the second-order rate constants for reactions of a number of phenoxide nucleophiles with substituted phenyl diphenylphosphate esters are linear across the range spanning the  $\text{pK}_a$  of the leaving group [56,57]. The  $k_{\text{nuc}}$  value when the leaving group is *p*-nitrophenol is 0.53, and is reduced to 0.12 when the leaving group is 2,4-dinitrophenol. The cumulative LFER data for aryl diphenyl and aryl diethyl phosphates indicate concerted mechanisms but with transition states that vary depending on the leaving group as well as the other ester moieties. It was concluded that a very loose or "exploded" transition state exists for attack of phenolate ions on 2,4-dinitrophenyl diphenylphosphate, a synchronous mechanism for triphenylphosphate, and a tighter, almost associative process for phenyl diethylphosphate [57].

$^{18}\text{O}$  isotope effects in the nonbridging oxygen atom and in the leaving group have been measured for a series of acyclic diethyl phosphate triesters with different leaving groups. A normal  $^{18}k_{\text{nonbridge}}$  isotope effect is observed in the reactions of all of the triesters, reflecting loss of double bond character to the P-O bond in the transition states for alkaline hydrolysis. The magnitude of this isotope effect increases from 1.0063 when the leaving group is *p*-nitrophenol ( $\text{pK}_a = 7.41$ ), to 1.025 for *p*-carbamoylphenol ( $\text{pK}_a = 8.6$ ), and 1.041 for the leaving group choline iodide ( $\text{pK}_a = 13.9$ ) [58]. The calculated isotope effect for reducing this bond from a double bond to a single bond is 1.04 [58]. The experimental values point to an increasingly associative transition state as the leaving group basicity increases. Unexpectedly, the primary  $^{18}\text{O}$  isotope effects in the scissile P-O bond also increase with leaving group basicity, from 1.006 with *p*-

nitrophenol, to 1.052 with the leaving group *m*-nitrobenzyl alcohol ( $\text{pK}_a = 14.9$ ) [58]. The large magnitudes were attributed to the imaginary frequency factor contribution to the isotope effect.

### Phosphorothioate Triesters

As with diesters, phosphorothioate triesters undergo hydrolysis more slowly than their oxygen counterparts. For example, triethyl phosphorothioate undergoes alkaline hydrolysis at  $31^\circ\text{C}$  12.4-fold more slowly than triethyl phosphate [59]. A similar thio effect of approximately 10 was also noted for a series of diethyl aryl phosphates and phosphorothioates [60]. A Brønsted analysis for the alkaline hydrolysis of the aryl esters gave respective  $\lg$  values of -0.43 and -0.35 for the phosphate and phosphorothioates [60]. These results were echoed in the primary  $^{18}\text{O}$  isotope effects in the alkaline hydrolysis reactions. In the phosphate triester with *p*-nitrophenol as the leaving group, this isotope effect is 1.0060, compared to 1.0045 in the phosphorothioate [61]. The two different experimental techniques both suggest bond fission to the leaving group is just slightly less advanced in the reactions of phosphorothioates compared to their oxygen analogs, and that despite the difference in rate, the transition states are very similar.

## 2. PHOSPHORYL TRANSFER FROM PHOSPHINATE AND THIOPHOSPHINATE ESTERS

Phosphinate esters do not occur naturally, but they are structurally related to phosphate and phosphonate esters that function as pesticides, neurotoxins and other biologically active substances [62]. A number of appropriately substituted phosphinic acids are effective metalloprotease inhibitors [63]. The chemistry of phosphinates, specially in relating structure and environmental factors to the mechanism of their reactions with nucleophiles, is therefore important from the perspective of understanding biologically important phosphoryl transfer processes. In the following sections, we review in broad outlines what is known from the literature on the nucleophilic reactions of phosphinate compounds.

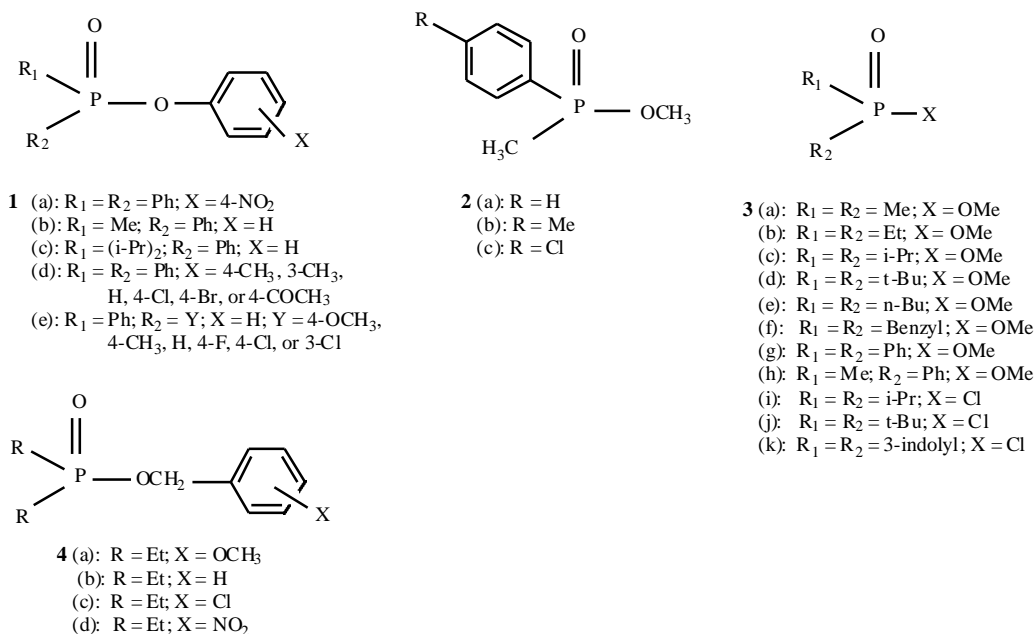


Fig. (11).

### Reactions in Acidic Media

Several studies of the hydrolysis of phosphinate esters in aqueous acidic ( $\text{H}_2\text{SO}_4$  or  $\text{HClO}_4$ ) media have been reported. A general feature of these reactions is the occurrence of a rate maximum in their rate profiles [64], which is consistent with the incidence of both acid catalysis and inhibition in a reaction sequence that involves water in the rate-determining step. Reaction in  $^{18}\text{O}$ -enriched water demonstrates [64a] P-O bond cleavage in **1a** (Figure 11) in an acid-catalyzed associative reaction that has a moderate negative  $S$  value (-27 eu.). Rate data for the hydrolysis of **2a-c** in  $\text{HClO}_4$  solutions were also interpreted [64b] on the basis of P-O bond cleavage *via* an associative mechanism. Although  $S$  values for the hydrolysis of **3a-d** in  $\text{D}_2\text{SO}_4$ - $\text{D}_2\text{O}$  are typically in the same range as observed for **2a** and **2b** (-18 to -21 eu.), the relative insensitivity of the reaction to substituent effects led to the suggestion [64c] that the substrates **3a-d** react *via* C-O bond cleavage. The  $\text{H}_2\text{SO}_4$ -catalyzed hydrolysis of the benzyl esters **4a-d** in  $\text{DMSO}$ - $\text{H}_2\text{O}$  mixture gives [64c] much less negative  $S$  values (-4 to -7 eu.); a Hammett  $\rho$  value of -3.5 and negative Bunnett  $\rho$  values in the range of -0.12 to -0.29 were calculated for these compounds. These results argue for a dissociative (A-1) mechanism involving C-O bond rupture. Significantly, no rate maximum was found in the reactions of **4b** and **4c**.

### Solvolyses of Phosphinyl Substrates in Other Media

The solvolysis reactions of a number of 1-arylethyl diphenylphosphinates (**5a-f**) (Figure 12) in aqueous ethanol obey first-order kinetics [65]; the rates of appropriately substituted substrates correlate well with  $\rho$  constants to give  $\rho = -5.10$ . These features substantiate a dissociative mechanism *via* C-O bond fission. Competition occurs between  $\text{S}_{\text{N}}1$  solvolysis and a basic hydrolysis mechanism involving P-O bond cleavage in the reaction of **5b**. An acid-catalyzed pathway is also present in the solvolysis of **5e** in unbuffered solutions.

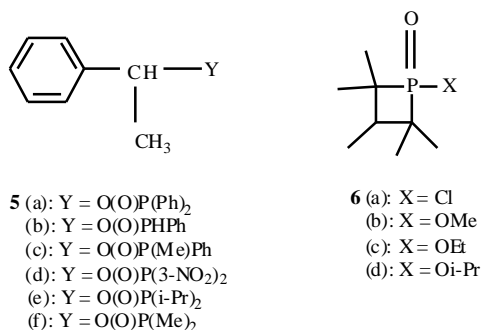


Fig. (12).

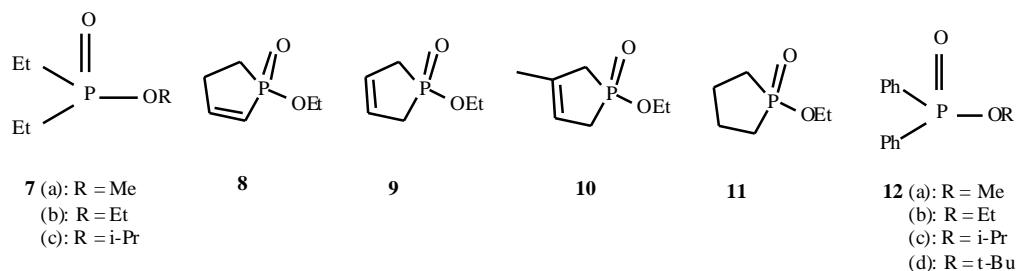


Fig. (13).

Haake's study of the solvolysis of the phosphinyl chlorides **3i-k** and **6a** in the ionizing solvents aqueous acetone, trifluoroacetic acid and formic acid solutions [66a] provides clear evidence for P-O bond cleavage *via* a dissociative ( $\text{S}_{\text{N}}1(\text{P})$ , or  $\text{D}_{\text{N}}+\text{A}_{\text{N}}$ ) mechanism for the reaction of the highly hindered di-*tert*-butylphosphinyl substrate **3j**. The reaction of the cyclic compound **6a** also occurs by a dissociative mechanism, with the incursion of nucleophilic participation. On the other hand, solvolysis of diisopropyl (**3i**) and di-3-indolyl phosphinyl (**3k**) chlorides are clear  $\text{S}_{\text{N}}2(\text{P})$  ( $\text{A}_{\text{N}}\text{D}_{\text{N}}$ ) displacements.

### Reactions of Phosphinate Esters with Strongly Basic Nucleophiles: Involvement of the Pentacoordinate Intermediate

By far, the bulk of the literature on the reactions of phosphinate esters deals with hydrolysis in basic media.  $^{18}\text{O}$  experiments show that alkaline hydrolysis of **1b** and **1c** occurs only by attack at phosphorus, and suggest no angular dependence of  $\rho$ -interaction between the Ph ring and the central P atom [66b]. Rate data for the hydrolysis of **1d** in 60% acetone-40%  $\text{H}_2\text{O}$  and **1e** in 35% dioxane-65%  $\text{H}_2\text{O}$  correlate well with Hammett constants to give  $\rho = 2.2$  and 0.7 for **1d** and **1e**, respectively. The 4- $\text{COCH}_3$  substituent showed significant deviation in the  $\log k$  vs.  $\text{pK}_{\text{a}}$  correlation for **1d**, indicating that significant negative charge is not developed in the reaction transition state [66c]. The widely differing values of  $\rho$  for the hydrolysis of these substrates suggest that they react by different mechanisms, as shown later in the discussion of the mechanistic significance of LFER correlations.

An early report [66d] compared reactivity of acyclic (**3a**, **b**, **e-h** and **7**) and cyclic phosphinates (**6b-d**, and **8-11**) (Figure 13); these compounds all undergo nucleophilic attack at the central P atom. The kinetic data for these substrates demonstrate qualitatively the importance of steric factors and provide the clue that the mechanism of reaction involves geometry that is different from an  $\text{S}_{\text{N}}2$  reaction at carbon. The retardation in rates observed in the hydrolysis of ethoxy analogs of **3b**, **3c** and **3d** provide kinetic evidence for steric hindrance. A more detailed study reported [67]  $\Delta H^\ddagger$  (12-16  $\text{kcal mol}^{-1}$ ) and  $\rho$  (*ca.* -30 eu.) values for some of these substrates. Angle strain accelerates the rate of reaction of **6b-d** relative to their acyclic analogs. The reaction is relatively insensitive to O-alkyl substitution; for **12**, the values  $\rho^* = 11$  and  $\rho = 0.6$  were measured. These reaction characteristics are consistent with an addition-elimination mechanism with rate-determining breakdown of the intermediate. This slow step is sensitive to the relative basicities of the nucleophile and the leaving group. When the substrate is **12d**, hydrolysis is a first-order elimination reaction with formation of isobutylene [68].

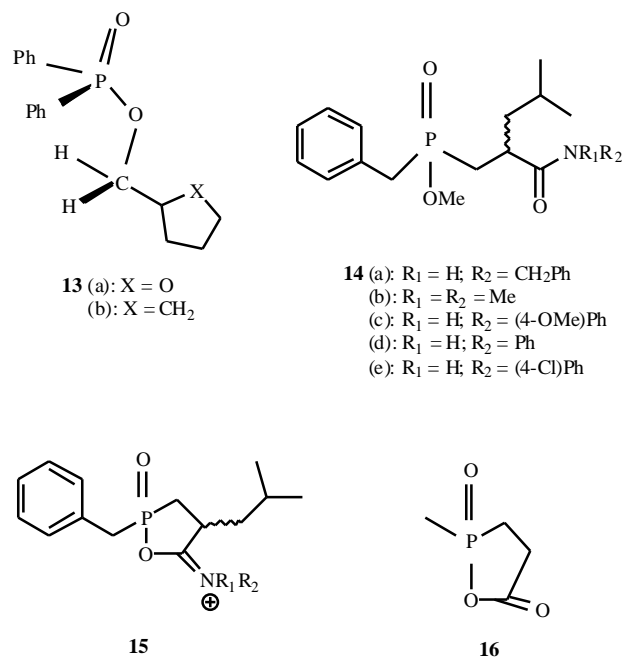
**Table 1.** Values derived from Hammett correlations for the reaction of phosphinates and thiophosphinates with hydroxide and alkoxide nucleophiles in various solvents at 25°C.

Reaction system	Solvent	Substituent Constant	$\rho$ value	Ref.
Ph <sub>2</sub> P(O)-OPhX/EtO <sup>-</sup>	EtOH	<sup>a</sup>	2.6	77
Ph <sub>2</sub> P(O)-OPhX/HO <sup>-</sup>	40% H <sub>2</sub> O-60% acetone		2.20	66b
Ph <sub>2</sub> P(O)-OPhX/HO <sup>-</sup>	H <sub>2</sub> O	<sup>o</sup>	1.40	70
Ph <sub>2</sub> P(O)-OPhX/HO <sup>-</sup>	50% H <sub>2</sub> O-50% EtOH	<sup>o</sup>	1.93	70
Ph <sub>2</sub> P(O)-OPhX/HO <sup>-</sup>	90% H <sub>2</sub> O-10% dioxane		1.55	69
Me <sub>2</sub> P(O)-OPhX/HO <sup>-</sup>	90% H <sub>2</sub> O-10% dioxane	<sup>-</sup>	0.93	74
Me <sub>2</sub> P(O)-OPhX/EtO <sup>-</sup>	EtOH	/ <sup>ob</sup>	2.69/2.77	78
Ph <sub>2</sub> P(S)-OPhX/HO <sup>-</sup>	50% H <sub>2</sub> O-50% EtOH	<sup>o</sup>	1.99	72
Ph <sub>2</sub> P(S)-OPhX/HO <sup>-</sup>	50% H <sub>2</sub> O-50% EtOH	<sup>o</sup>	1.90	73
Ph <sub>2</sub> P(O)-SPhX/HO <sup>-</sup>	80% H <sub>2</sub> O-20% MeOH		1.46	71
Me <sub>2</sub> P(S)-OPhX/HO <sup>-</sup>	H <sub>2</sub> O	<sup>o</sup>	1.28	75, 76
Me <sub>2</sub> P(S)-OPhX/HO <sup>-</sup>	50% H <sub>2</sub> O-50% EtOH	<sup>o</sup>	1.72	75, 76
Ph(Me)P(S)-OPhX/HO <sup>-</sup>	50% H <sub>2</sub> O-50% EtOH	<sup>o</sup>	1.83	75
Ph(MeSO <sub>2</sub> CH <sub>2</sub> )P(O)-OPhX/HO <sup>-</sup>	80% H <sub>2</sub> O-20% dioxane		1.45	79

<sup>a</sup> Normalized value of  $\rho$  ( <sup>a</sup> ) = 1.3<sup>b</sup> Normalized value of  $\rho$  ( <sup>b</sup> ) = 1.37

The mechanism for the hydrolysis of phosphinates in aqueous solution and in binary aqueous solvents is well established to involve a pentacoordinate intermediate. In systems with substituted phenoxides or thiophenoxides as leaving groups such as R<sub>2</sub>P(O)-OPhX, R<sub>2</sub>P(S)-OPhX, and R<sub>2</sub>P(O)-SPhX (see Table 1) reaction rates correlate well with <sup>o</sup> or <sup>o</sup> substituent constants [66b, 69-76], as also found for the ethanolysis of Ph<sub>2</sub>P(O)-OPhX [77] and Me<sub>2</sub>P(O)-OPhX [78] in anhydrous ethanol. The rates of the alkaline hydrolysis of the aryl (methylsulfonyl)methylphenylphosphinates Ph(CH<sub>3</sub>SO<sub>2</sub>CH<sub>2</sub>)P(O)-OPhX also exhibit a good Hammett  $\rho$ -relationship [79]. Correlation of rates with <sup>o</sup> substituent constants is good evidence that the incoming charge from the nucleophile is not delocalized onto the leaving group O in the transition state of the reaction, which implicates rate-limiting formation of the pentacoordinate intermediate. The apparent exception to this general trend in (Table 1) is the hydrolysis of substituted phenyl dimethylphosphinates, Me<sub>2</sub>P(O)-OPhX, which is correlated with <sup>-</sup> substituent constants, consistent with a concerted S<sub>N</sub>2(P)-type mechanism [74]. The magnitude of  $\rho$  values in (Table 1) and their possible use as a diagnostic mechanistic tool are discussed below.

The concept of *conformational transmission* in pentacoordinate phosphorus compounds [80] holds that certain substituents facilitate the pseudorotation of P(V) trigonal bipyramidal intermediates. This concept has been applied to the mechanism of nucleophilic substitution reactions of phosphinates [81]. The alkyl diphenylphosphinates **13a** and **13b** (Figure 14) were reacted with MeO<sup>-</sup> in methanol solvent under identical conditions [82]. The rate ratio  $k_{14a}/k_{14b} = 20$  observed for the reactions shows that the compound which incorporates the POCCO atomic sequence in its structure (**13a**) reacts faster than its counterpart in which this fragment is absent. This rate difference is ascribed to the conformational transmission effect, which occurs in the transition state for the formation of the pentacoordinate intermediate [82].

**Fig. (14).**

Imidazole catalyzes the hydrolysis of both Me<sub>2</sub>P(O)-OPhX [69] and Ph<sub>2</sub>P(O)-OPhX [74] by different mechanisms. While catalysis in the Me<sub>2</sub>P(O)-OPhX system is of the general base type [69], nucleophilic catalysis has been demonstrated for Ph<sub>2</sub>P(O)-OPhX [74]. This difference in the catalytic mechanism of imidazole has its origin in steric crowding which is present in the transition state for the hydrolysis of Ph<sub>2</sub>P(O)-OPhX substrates [69, 74]. Hydrolysis of the sterically hindered methyl diisopropylphosphinate **3c** has been shown by mass spectrometric and NMR experiments in <sup>18</sup>O labeled H<sub>2</sub>O to involve a pathway with C-O bond cleavage which accounts for 25% of the substitution reaction [83].

Recent work on the reactivity of phosphinate esters include the hydrolysis of 1-oxo-2-oxa-1-phosphabicyclo[2.2.2]octane, which hydrolyzes 2 orders of magnitude faster than its phosphate analog [84]. This rate difference is attributed to the greater ease with which the phosphinate achieves the five-coordinate transition state relative to the phosphate. The  $10^3$ -fold rate difference between 1-oxo-2-oxa-1-phosphabicyclo[2.2.2]octane and its acyclic analog,  $\text{Et}_2\text{P}(\text{O})\text{-OEt}$  [85, 86] is suggested to have its origin in solvation effects [84]. The latter compound also reacts by rate-limiting formation of the pentacoordinate intermediate.

Hydrolysis of the  $\alpha$ -carboxamido-substituted phosphinates **14** is acid catalyzed and was shown [87] to be facilitated by the presence of the amide in a trend that depends on the amide electron density, suggesting the intermediacy of the cyclic imidate structure **15**. A mixed anhydride species **16** has also been postulated as an intermediate in the acidic and alkaline cleavage of methyl  $\alpha$ -carboxyphosphinates [88]. These cyclic intermediates are conceivably formed from pentacoordinate precursors.

### Reactions with Other Nucleophiles

Whereas  $\text{Ph}_2\text{P}(\text{O})\text{-OPhX}$  esters hydrolyze by a pentacoordinate intermediate ( $\text{A}_\text{N} + \text{D}_\text{N}$ ) mechanism [66b, 69, 70], their reaction with substituted phenoxides in water is a concerted one, as demonstrated by its Brønsted characteristics [89]. This change in mechanism is due to the weaker basicity of phenoxides relative to  $\text{HO}^-$  as nucleophiles [54, 74, 78, 89-91]. Nucleophilic catalysis has been demonstrated for the reaction of  $\text{Ph}_2\text{P}(\text{O})\text{-OPhX}$  ( $\text{X} = 4\text{-NO}_2$ ) with imidazole in acetonitrile; with benzoate, the reaction proceeds *via* the formation of an anhydride intermediate [92]. Aminolysis of  $\text{Ph}_2\text{P}(\text{O})\text{-OPhX}$  ( $\text{X} = 4\text{-NO}_2$ , 4-CN, 3- $\text{NO}_2$ ),  $\text{Ph}_2\text{P}(\text{S})\text{-OPhX}$  ( $\text{X} = 4\text{-NO}_2$ ),  $\text{Ph}_2\text{P}(\text{O})\text{-SPhX}$  ( $\text{X} = 4\text{-NO}_2$ ) and  $\text{Ph}_2\text{P}(\text{S})\text{-SPhX}$  ( $\text{X} = 4\text{-NO}_2$ ) by primary and secondary amines and a series of diamines occurs by rate-limiting decomposition of a zwitterionic pentacoordinate intermediate [93]. Both *n*- $\text{BuNH}_2$  and the diamines investigated exhibit general base catalysis of the reaction.

Rearrangement of diastereomerically enriched *N*-phosphinoyl-*O*-sulfonylhydroxylamine (**17**) with  $\text{RNH}_2$  ( $\text{R} = \text{CH}_3$ , *t*-Bu) gives **19** (Scheme 1). The reaction occurs with retention of configuration [94]. The mixed anhydride **18** results from base-promoted rearrangement of **17** in a process that occurs with inversion of configuration at phosphorus. This is followed by nucleophilic substitution by a second amine molecule in a concerted reaction. The occurrence of a dissociative elimination-addition pathway ( $\text{D}_\text{N} + \text{A}_\text{N}$ ) is supported by observed departures from complete stereospecificity of the reaction. On the other hand, a three-coordinate methylenethioxophosphorane intermediate has been proposed [95] for the nucleophilic substitution of 4-nitrobenzyl thiophosphinyl chloride by  $\text{Et}_2\text{NH}$ , based on the

observed incorporation of deuterium in the benzylic methylene group with  $\text{Et}_2\text{ND}$  as the nucleophile.

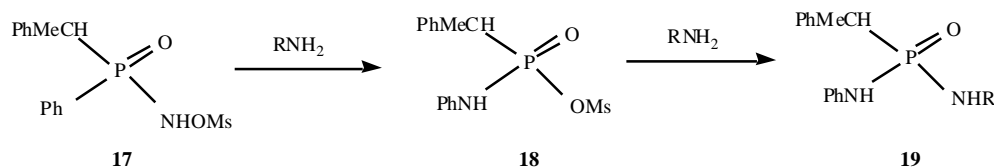
### Mechanistic Insights from Linear Free Energy Relationships

Correlation of rates of substitution reactions of the phosphinates in (Table 1) with  $\rho$  or  $\rho^\ddagger$  substituent constants formed the basis for concluding that the mechanism of these substrates is of the associative type, involving rate-limiting formation of a pentacoordinate intermediate [66b, 66-76]. The values of  $\rho$  in these reactions (Table 1) are moderately large, ranging from 1.4 to 2.8 in the various solvents, mainly aqueous or predominantly aqueous binary solvent mixtures. Normalizing the  $\rho$  value in solvents other than water according to the expression  $\rho_\text{w} = \rho / \rho_\text{eq}$  gives values generally in the range 1.3 - 1.6 [78]. The hydrolysis of  $\text{Ph}(\text{CH}_2\text{SO}_2\text{CH}_2)\text{P}(\text{O})\text{-OPhX}$  in 80% water-20% dioxane [79] gives  $\rho = 1.45$ ; this falls within the range given above. These values of  $\rho$  are substantially higher than  $\rho^\ddagger = 0.93$  reported for the hydrolysis of dimethylphosphinates [74]. It thus appears that the magnitude of  $\rho$  could be used diagnostically, at least in a qualitative sense, to distinguish between a concerted and stepwise mechanism [71, 75]. The larger magnitude of  $\rho$  for rate-limiting pentacoordinate intermediate formation, compared with the smaller value reported for the concerted mechanism [74], results from a more effective transmission of the electronic effect of substituents on the leaving group aryl moiety through the intact P-O bond in the transition state for the former process [78]. According to Jencks [96], the magnitude of  $\rho$  is also a measure of the total amount of bonding to the central atom in the transition state.

The Brønsted parameters  $\rho_\text{nuc}$ ,  $\rho_\text{lg}$ , and the derived  $\rho_\text{eq}$  values of 0.46, -0.79, and 1.25, respectively, for the reaction of aryl diphenylphosphinates [ $\text{Ph}_2\text{P}(\text{O})\text{-OPhX}$ ] with phenoxides in water have been used to characterize a concerted mechanism for the reaction [89]. The transition state structure was deduced to have considerable  $\text{Ph}_2\text{PO}^+$  character from the effective charge distribution [97].

Conflicting conclusions on the mechanism of the hydrolysis of the phosphinothioates  $\text{Me}_2\text{P}(\text{S})\text{-OPhX}$ ,  $\text{MePhP}(\text{S})\text{-OPhX}$ , and  $\text{Ph}_2\text{P}(\text{S})\text{-OPhX}$  in water and water-ethanol mixtures are reached by a consideration of Hammett and Brønsted-type correlations of the rates of the reactions of these substrates. These compounds correlate well with  $\rho$  or  $\rho^\ddagger$  substituent constants, consistent with an associative mechanism involving rate-limiting formation of a pentacoordinate intermediate [72, 75]. On the other hand, Brønsted  $\rho_\text{lg}$  values for these reactions are in the range of -0.30 to -0.50 [72, 75]; these  $\rho_\text{lg}$  values indicate little-to-moderate detachment of the leaving group in the transition state of a concerted reaction [89].

We have recently [98] studied the reaction of  $\text{Me}_2\text{P}(\text{S})\text{-OPhX}$  esters with  $\text{HO}^-$ , alcoholates ( $\text{RO}^-$ ) and phenoxides



Scheme 1.

(PhO<sup>-</sup>) as nucleophiles in aqueous solution, in which the number of substituents on the aryl leaving group utilized in the LFER constructions is reasonably large. A Brønsted-type plot of  $\log k_{\text{nuc}}$  vs.  $pK_{\text{a}}$  of nucleophile is linear for the phenoxides ( $\rho_{\text{nuc}} = 0.46$ ) but curved in the region of the highly basic RO<sup>-</sup> and HO<sup>-</sup> nucleophiles ( $\rho_{\text{nuc}} = 0.07$ ). The  $\log$  value is the same for the nucleophilic reactions of phenoxide (-0.53) and HO<sup>-</sup>/alcoholates (-0.52). We obtained a significantly better Hammett correlation of rates with  $\rho_{\text{nuc}}$  rather than with  $\rho_{\text{O}}$  constants, with  $\rho_{\text{nuc}} = 1.18 \pm 0.07$  and  $1.09 \pm 0.07$  for HO<sup>-</sup> and PhO<sup>-</sup> nucleophiles, respectively, of the same order as 0.93 measured by Williams for the hydrolysis of the P=O analog [74]. These results are fully consistent with a concerted reaction that lies slightly on the dissociative side, which also exhibits abnormal solvation for the highly basic nucleophiles.

### Alkali Metal Ion Catalysis in the Nucleophilic Reactions of Phosphinate Esters

Considerable attention has been directed toward the study of metal ion effects on phosphoryl transfer reactions involving phosphate esters. By contrast, investigations of metal ion effects in the reactions of phosphinate esters have been few. What is presently known in this domain comes from the work of Buncl and his group, who have studied the influence of alkali metal ions on the nucleophilic displacement reactions of a number of phosphinates in ethanol [77, 78, 99, 100].

Ethanolysis of Ph<sub>2</sub>P(O)-OPhX [77, 96] and Me<sub>2</sub>P(O)-OPhX [78] and the reaction of Ph<sub>2</sub>P(O)-OPhX with phenoxide [100] in anhydrous ethanol are catalyzed by alkali metal ion which demonstrate the selectivity order Li<sup>+</sup> > Na<sup>+</sup> > K<sup>+</sup>. The nucleophilic reactions of these substrates in ethanol have been shown to react by rate-determining formation of the pentacoordinate intermediate [77, 78]. Ground state and transition state stabilization by the metal ions was quantified in each case and the mode of stabilization was shown to be electrostatic in nature, manifesting an inverse relationship with crystal radii [77]. The selectivity order observed in these reactions has been related to the selectivity patterns of alkali metal cations for ion-exchange resins and glass electrodes according to Eisenman's theory of ion-exchange selectivity [101]. The order results from the dominance of electrostatic interactions over solvent rearrangement in the nucleophilic reactions of phosphorus esters, contrasting with the reverse order observed for sulfonate esters where the dominant effect is solvent rearrangement [77b, 102, 103]. The magnitude of catalysis is greater for the reactions of Ph<sub>2</sub>P(O)-OPhX esters when compared with their Me<sub>2</sub>P(O)-OPhX counterparts, a consequence of dissimilar transition states for the catalyzed reactions in the two series of compounds [78].

### Effect of S-Substitution on the Reactivity of Phosphinate Esters

Generally speaking, phosphate esters are more reactive than their thio analogs. Several reasons have been adduced for this order of reactivity, mainly based on the electronegativity differences between O and S, favoring O. As a consequence, several proposals have been made to rationalize the reactivity difference: oxygen stabilizes the developing positive charge at the P center better than S

[104]; the thioanion exhibits poorer electron-donating ability relative to the oxyanion in expelling the leaving group [104]; the higher electrophilicity of phosphorus in P=O than in P=S [105]; the disparity in the polarization of phosphoryl and thiophosphoryl bonds, favoring the former [105c]; structural differences between P=O and P=S moieties, which includes interatomic distances and van der Waals radii [106].

Data for such comparisons in the same solvent in the phosphinate ester series are limited. Cook and co-workers [107] have reported a small rate-retarding effect, less than a factor of 10, for the replacement of O by S in a series of alkyl phosphinates. An effect of similar magnitude was also found for the hydrolysis of (ClCH<sub>2</sub>)<sub>2</sub>P(O)-OEt and its thio analog, while rate ratios  $k_{\text{P=O}}/k_{\text{P=S}} < 1$  have been reported for the hydrolysis of Et<sub>2</sub>P(O)-OEt and Et<sub>2</sub>P(S)-OEt [108] and similar substrates [107]. In aryl phosphinates, comparison of the results of Douglas and Williams [108] with our recent data [98] gives the rate ratio  $k_{\text{P=O}}/k_{\text{P=S}} = 2.4$  for Me<sub>2</sub>P(O)-OPhX (X = NO<sub>2</sub>) and its thio analog. Evidently, phosphinate esters are less sensitive to S-substitution in the P=O bond than phosphates. Greater rate differences are obtained in alkyl phosphinates [107] when the bonding to the leaving group is changed from P-O to P-S. In such situations, phosphinates with thiolate leaving groups react much faster than their alcoholate counterparts, reflecting the lower basicity of RS<sup>-</sup> relative to RO<sup>-</sup>. Comparison of the hydrolysis rates in the aryl phosphinates Ph<sub>2</sub>P(O)-YPhX (X = NO<sub>2</sub>, Y = O or S) in binary aqueous solvents [89, 107] gives a relatively low rate ratio of  $k_{\text{P=O}}/k_{\text{P=S}} = 4.3$ . A systematic study is thus required in order to understand the trend of reactivity in these substrates.

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