Other Phosphazene–Platinum Derivatives. Although the structures of high polymeric $(PtCl_2)_x[NP(NHCH_3)_2]_n$ and $PtCl_2[N_4P_4(CH_3)_8]$ have not been obtained by x-ray diffraction techniques, their structure can tentatively be deduced by analogy. Thus, $PtCl_2[N_4P_4(CH_3)_8]$ is expected to contain a square planar cis platinum unit bonded to the skeletal ring nitrogen atoms. A similar situation is envisaged for $(PtCl_2)_x[NP(NHCH_3)_2]_n$. However, in this case the average number of phosphazene repeat units in the polymeric loop between the coordinated nitrogen atoms is at present unknown. This cis configuration at platinum appears to be retained in view of spectral evidence and the anticancer activity of the complex.[2]

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Supplementary Material Available: Table III, a listing of observed and calculated structure factor amplitudes (9 pages). Ordering information is given on any current masthead page.

References and Notes

(1) This paper is part 31 in a series on phosphorus–nitrogen compounds.
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Hydration and Dehydration of Phosphoric Acid Derivatives: Free Energies of Formation of the Pentacoordinate Intermediates for Phosphate Ester Hydrolysis and of Monomeric Metaphosphate

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Abstract: The heat of hydrolysis for pentaethoxyphosphorane is −17.75 ± 0.45 kcal mol^{-1} for the process: $P(OEt)_5(l) + H_2O(l) = PO(OEt)_3(aq) + 2EtOH(aq)$. From this may be derived the free energies of formation in aqueous solution of $P(OEt)_n(OH)_{5-n}$ (n, $\Delta G_f°$ (kcal/mol^{-1}): 5, −232 ± 3; 4, −249 ± 3; 3, −266 ± 3; 2, −281 ± 3; 1, −298 ± 3; 0, −314 ± 3). These permit the calculation of the free energy changes for the addition of water to phosphoric acid and its esters. Comparison with the results of earlier kinetic studies reveals surprisingly high barriers to breakdown of the pentacoordinate intermediates in phosphoryl transfer reactions. A kinetic argument leads to a value for the free energy of dehydration of orthophosphoric acid to monomeric metaphosphoric acid in aqueous solution of 32 ± 2 kcal mol^{-1}. These data permit comparison of the behavior of orthophosphate derivates toward addition and elimination. The intrinsic barrier for addition of hydroxide ion to phosphate esters is much greater than for the analogous addition to carbonyl compounds.

Despite their considerable interest to organic and biochemistry, the study of the mechanisms of phosphoryl group reactions has lagged behind that of acyl group reactions. In part this is due to the slowness of many phosphoryl transfer reactions; in part it is due to the greater mechanistic versatility of phosphoric acid derivatives relative to carboxylic acid derivatives.[2] Simple alkyl esters of phosphoric acid may undergo hydrolysis by nucleophilic attack at phosphorus, nucleophilic attack at carbon, or elimination of alcohol to give a transient metaphosphate intermediate.[2] By contrast simple esters of carboxylic acids ordinarily react by nucleophilic attack at the carbonyl[3] and only rarely by attack at the ester carbon[3] or by elimination to give a ketene intermediate.[4] For reactions of carboxylate esters by the usual mechanism, nucleophilic attack at carbonyl carbon, the tetrahedral intermediate which is normally postulated, has well known and quite stable (in the absence of acid) alkyl derivatives in the ortho esters. By contrast the analogues of the intermediates for reaction by nucleophilic attack at phosphoryl phosphorus, the pentaalkoxyphosphoranes, have only recently been prepared, and are usually rather reactive.[5]

Recently it was shown that the free energy levels of the intermediates in acyl transfer reactions could be evaluated by determining the free energy level in aqueous solution of the ortho ester analogue of the intermediate and making use of the fact that ΔG for the reaction

$$C\text{-}OH + CH_3OH \rightleftarrows C\text{-}OCH_3 + H_2O$$

Table I. Thermodynamic Data[a]

Compd	$\Delta H_f°(g)^{b}$	$S°(g)^{c}$	$\Delta G_f°(g)^{b}$	$\Delta H_v^{b,d}$	$\Delta H_f°(l)^{b}$	$\Delta H_s^{b,e}$	$\Delta H_f°(aq)^{b,f}$	$\Delta G_f°(aq)^{b}$
H_2O	-57.80^{g}	45.11^{g}	-54.68^{g}		-68.32^{g}			$-56.69^{g,h}$
CH_3CH_2OH	-56.24^{g}	67.4^{g}	-40.30^{g}		-66.42^{m}	-2.43^{l}	-68.85^{n}	-43.31^{i}
H_3PO_4							-309.35 ± 0.38^{j}	-274.22 ± 0.48^{k}
$CH_3CH_2OPO_3H_2$							-307 ± 1^{o}	-257 ± 1^{o}
$(CH_3CH_2O)_2PO_2H$							-305 ± 1^{o}	-241 ± 2^{o}
$(CH_3CH_2O)_3PO$	-284.5^{m}	131.4^{o}	-219.12^{n}	13.7^{m}	-298.2^{m}	-5.05^{p}	-303 ± 1^{n}	-223 ± 2^{o}
$P(OH)_5$							-367 ± 2^{o}	-314 ± 3^{o}
$(CH_3CH_2O)P(OH)_4$							-366 ± 2^{o}	-298 ± 3^{o}
$(CH_3CH_2O)_2P(OH)_3$							-366 ± 2^{o}	-281 ± 3^{o}
$(CH_3CH_2O)_3P(OH)_2$							-365 ± 2^{o}	-266 ± 3^{o}
$(CH_3CH_2O)_4P(OH)$							-364 ± 2^{o}	-249 ± 3^{o}
$(CH_3CH_2O)_5P$	-338.17^{n}	176.20^{o}	-238.01^{n}	16.7^{o}	-354.84^{p}	-8.05^{o}	-363 ± 1^{o}	-232 ± 3^{o}
HPO_3								-186 ± 2^{o}
$CH_3CH_2OPO_2$								-170 ± 2^{o}

[a] At 25 °C, standard states are ideal gas at 1 atm, pure liquid, and 1 M aqueous solution with an infinitely dilute reference state, unless otherwise noted. [b] In kcal mol^{-1}. [c] In cal deg^{-1} mol^{-1}. [d] Heat of vaporization. [e] Heat of solution, liquid to infinitely dilute aqueous solution, unless otherwise noted. [f] Standard state is infinitely dilute aqueous solution. [g] Reference 41. [h] Standard state is the pure liquid. [i] Reference 42. [j] Reference 43. [k] Calculated from $\Delta H_f°(aq)$ using a value for $S°(aq)$ given in ref 44. [l] Reference 45. [m] Reference 46. [n] Calculated from values in this table. [o] Calculated as described in the text. [p] This work.

is *small* and insensitive to the substituents on C.[6] It seemed interesting and worthwhile to explore the possibility that this approach could be applied to the intermediates in phosphoryl transfer reactions.

To this end, the heat of hydrolysis of pentaethoxyphosphorane has been determined, and from this have been calculated the free energy levels of the intermediates in the hydrolysis of simple alkyl esters of phosphoric acid.

Results

Heat of Formation of Pentaethoxyphosphorane. Pentaethoxyphosphorane was prepared and purified by the method of Denney et al.[5c] Analysis by 100-MHz NMR showed that the purified phosphorane contained 7% triethyl phosphate and 4% propylene carbonate (used to extract the bulk of the triethyl phosphate by-product). This was not improved by an additional extraction using propylene carbonate. Hydrolysis in D_2O gave triethyl phosphate and ethanol as the only detectable products (100-MHz ^1H NMR).

The heat of hydrolysis was determined calorimetrically; suitable corrections were made for the heats of solution of the impurities. The value obtained was -17.75 ± 0.45 kcal mol^{-1} for the reaction

$$P(OEt)_5(l) + H_2O(l) = PO(OEt)_3(aq) + 2EtOH(aq) \quad (1)$$

Using the thermochemical values for water, triethyl phosphate, and ethanol found in Table I, a value of -354.86 ± 1.32 kcal mol^{-1} was calculated for the heat of formation of liquid pentaethoxyphosphorane.

To obtain the heat of formation in aqueous solution of pentaethoxyphosphorane it is necessary to estimate the heat of solution. Because of the low solubility and rapid hydrolysis of the phosphorane it is unlikely that this quantity will be measurable. Examination of models suggested that each of the five ethoxy groups in pentaethoxyphosphorane has about the same amount of room as each of the four ethoxy groups in tetraethyl orthocarbonate. Accordingly, it appeared reasonable that the heat of solution of the phosphorane could be estimated as $5/4$ of the heat of solution of the orthocarbonate. The low solubility of the orthocarbonate makes it difficult to obtain a precise value of the heat of solution, but this is ca. -6 kcal mol^{-1}.

A better value can be calculated from the readily measurable heat of solution of tetramethyl orthocarbonate, -3.71 ± 0.44 kcal mol^{-1}, assuming additivity of heats of solution. In Table II are found data supporting a value of -0.68 ± 0.07 kcal mol^{-1} for the increment in heat of solution when methoxyl is replaced by ethoxyl. Using this value, a heat of solution of -6.44 ± 0.46 kcal mol^{-1} for tetraethyl orthocarbonate can be calculated, and hence a value of -8.05 ± 0.58 kcal mol^{-1} for the heat of solution of pentaethoxyphosphorane. Finally a value of -362.90 ± 1.48 kcal mol^{-1} can be calculated for the heat of formation in aqueous solution of pentaethoxyphosphorane.

Table II. Increment in Heat of Solution when Methoxyl is Replaced by Ethoxyl

Compd	$\Delta H_{soln}{}^{a}$	$\Delta\Delta H_{soln}{}^{b}$ per alkyl group
MeOH	-1.75 ± 0.007^{c}	-0.68 ± 0.01
EtOH	-2.43 ± 0.01^{c}	
$MeOCH_2CH_2OH$	-3.65 ± 0.05^{d}	-0.68 ± 0.05
$EtOCH_2CH_2OH$	-4.34 ± 0.007^{d}	
$MeOCH_2CH_2OMe$	-5.49 ± 0.007^{d}	-0.77 ± 0.01
$EtOCH_2CH_2OMe$	-6.26 ± 0.01^{d}	-0.60 ± 0.01
$EtOCH_2CH_2OEt$	-6.84 ± 0.01^{d}	
MeOAc	-1.89 ± 0.10^{e}	-0.30 ± 0.10
EtOAc	-2.19 ± 0.02^{f}	
MeOCHO	-0.85 ± 0.05^{e}	-0.79 ± 0.35
EtOCHO	-1.64 ± 0.34^{g}	
$CH_2(OMe)_2$	-3.20 ± 0.53^{g}	-0.49 ± 0.31
$CH_2(OEt)_2$	-4.18 ± 0.32^{g}	
$(MeO)_3PO$	-2.97 ± 0.06^{h}	-0.69 ± 0.02
$(EtO)_3PO$	-5.05 ± 0.02^{h}	

[a] Enthalpy of solution in water at 25 °C, in kcal mol^{-1}. [b] Increment in ΔH_{soln} when OMe is replaced by OEt. [c] Reference 47. [d] Reference 48. [e] Reference 40. [f] Reference 49. [g] This work. [h] Reference 52.

Free Energy of Formation of Pentaethoxyphosphorane. The most useful thermodynamic quantity for pentaethoxyphosphorane is the free energy of formation in aqueous solution. Unfortunately the calculation is lengthy and cumulation of errors is a serious problem. In the absence of any vapor pressure data, the heat of vaporization can only be estimated from correlations based on molecular structure. By an adaptation of Laidler's method[7,8] based on bond contributions, the heat of vaporization for $P(OEt)_5$ can be estimated from that of $P(OEt)_3$ as 16.7 ± 2 kcal mol^{-1}. This leads to a value of -338.19 ± 2.4 kcal mol^{-1} for the heat of formation of gaseous $P(OEt)_5$. The standard entropy of this species can be estimated by Benson's atom contributions approach.[9] The value for pentacoordinate phosphorus was obtained from literature values of $S°$ for PCl_5[9b] and PF_5[9b] in combination with the contributions recommended for Cl or F.[9a] The value of $S°(g)$ so obtained for $P(OEt)_5$ is 176.2 ± 5 cal deg^{-1} mol^{-1}, which leads to a value of -230.7 ± 2.8 for $\Delta G_f°(g)$.

The free energy of transfer from gas phase to solution can reasonably be estimated as ⅚ of the free energy of transfer for tetraethyl orthocarbonate (see Experimental Section), or -1.12 ± 0.20 kcal mol^{-1}. This procedure is justified by the additivity shown by free energies of transfer[17] and the similar nature of the exposed portions of the two compounds. Finally one obtains an estimated value for the free energy of formation of $P(OEt)_5$ in aqueous solution of -231.8 ± 2.9 kcal mol^{-1}.

Heats of Formation of Hydroxyethoxyphosphoranes. It has been shown that the free energy change for the reaction

$$>\mathrm{C{-}OR} + H_2O \rightarrow\ >\mathrm{C{-}OH} + \mathrm{ROH}\ (\mathrm{R} = CH_3 \text{ or } CH_2CH_3) \qquad (2)$$

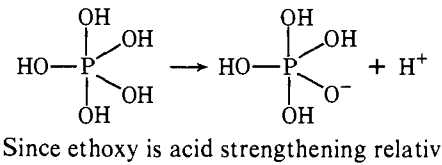
is always small[6,10] and that such variations as are found can be attributed to symmetry effects, steric crowding, and, with a small ρ^* value, to effects of electron withdrawal by the substituents on the central carbon. Since the acidity of an alcohol is also determined by the electron withdrawing properties of the substituents[11] it follows that the electronic effect on the equilibrium constant for reaction 2 could equally well be expressed in terms of the pK_a of the alcohol rather than the sum of the σ^* values of the substituents. In Figure 1 is shown a plot of the available data for $\Delta G''$ as a function of the pK_a of XOH for reactions of the form:

$$\mathrm{XOH} + \mathrm{ROH} = \mathrm{XOR} + H_2O \qquad (3)$$

In these reactions XOR is an ether, acetal, or hemiacetal, or else an orthophosphate species. Figure 1 shows that $\Delta G''$ correlates with pK_a, and that orthophosphate esters obey the same relationships as ethers. Carboxylate esters do *not* obey the relationship, presumably because the pK_a is strongly influenced by improved resonance stabilization of the conjugate base. For orthophosphates, where resonance stabilization of the conjugate base is less important, the pK_a is a measure of electron withdrawal in the conjugate acid. The best line fitting the data is described by[10,12]

$$\Delta G'' = +(4.78 \pm 0.28) - (0.336 \pm 0.024)pK_a \qquad (4)$$

Needless to say, no pK_a values for oxyphosphoranes are available. Fortunately only approximate values are needed, and a value for pentahydroxyphosphorane can be estimated by the method of Branch and Calvin[13] as shown in eq 5.



$pK_a = 8.5$ (5)

Since ethoxy is acid strengthening relative to hydroxy the alkoxyhydroxyphosphoranes are expected to be more acidic; the magnitude of this effect is estimated from the pK_a differences between phosphoric acid and its mono- and dialkyl esters; see Table VI.

Symmetry effects on reaction 3 can be estimated relatively straightforwardly, the only complication being the question of which sort of ethoxy (basal or axial) will be replaced first. On the basis of the known preference for more electronegative groups to be axial,[14] and the known greater σ^* values for ethoxyl than for hydroxyl,[15] it was assumed that the three basal ethoxyls were replaced first.

In the absence of any quantitative studies of nonbonded interactions in pentacoordinate species, it was necessary to make the rather crude assumption that crowding is similar to that in tetraethyl orthocarbonate. Fortunately this interaction is very small,[10] so even a large percentage error will have a very small effect on the overall results.

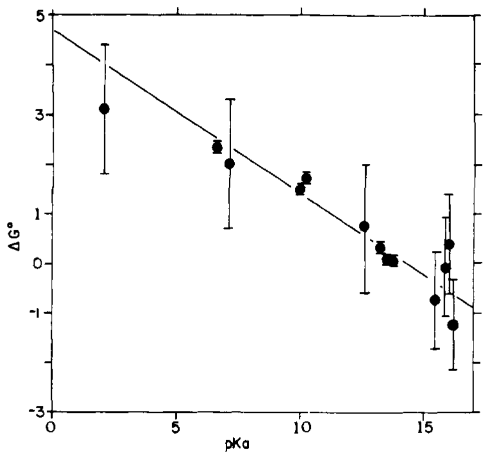


Figure 1. Free energy change for reaction 3 as a function of pK_a. XOH, $\Delta G_3''$, pK_a: CH_3OH, −0.75,[11] 15.49;[12] CH_3CH_2OH, −0.07,[11] 15.93;[12] $(CH_3)_2CHOH$, 0.39,[11] 16.10;[12] $(CH_3)_3COH$, −1.35,[11] 16.04;[12] $CH_3CHOHOH$, 0.06,[11] 13.57;[74] $(CH_3)_2CHCHOHOH$, 0.06,[11] 13.77;[74] CH_2COHOH, 0.33,[11] 13.27;[74] $CF_3CHOHOH$, 1.75,[11] 10.20;[74] $C_6H_5C(CF_3)(OH)OH$, 1.49,[11] 10.00;[74] $(CF_3)_2COHOH$, 2.35,[11] 6.58;[74] H_2PO_3OH, 3.12 ± 1.29, 2.12; HPO_3^--OH, 2.01 ± 1.29, 7.21; PO_3^{2-}-OH, 0.74 ± 1.29, 12.67. The line was fitted by weighted least squares.

Table III. Entropy Changes for Reaction 3

Example[a]	$\Delta G°$[b]	$\Delta H°$[b]	$\Delta S°$[c]	ΔS^*[c,d]
$CH_3C(=O)OCH_2CH_3 + H_2O$	−1.66[e]	0.13[f]	6.01	4.63
$HC(=O)OCH_3 + H_2O$	−1.25[g]	0.16[h]	4.73	3.35
$CH_2CH_2OCH_2CH_3 + H_2O$	−0.60[i]	2.02[j]	8.79	6.03

[a] Standard state for reactants and products is 1 M aqueous solution with an infinitely dilute reference state except for water, where the standard state is the pure liquid. [b] In kcal mol^{-1}. [c] In cal deg^{-1} mol^{-1}. [d] Corrected for symmetry. [e] Reference 50. [f] Calculated from the heat of reaction with pure liquid standard states[51] and the heats of solution of ethyl acetate,[49] acetic acid,[53] and ethanol.[54] [g] Reference 55. [h] This work. [i] Reference 56. [j] Calculated from the heats of formation of products and reactants[46] and the heats of solution of diethyl ether[57] and ethanol.[54]

Finally there is the problem that the enthalpy of formation of pentaethoxyphosphorane is more reliable than the free energy of formation. To overcome this problem it is necessary to estimate the entropy change for reaction 2. The available data are collected in Table III. Using these data, an average value of $\Delta S_2^* = 4.67 \pm 1.34$ is obtained, which permits eq 4 to be transformed to[12]

$$\Delta H'' = +(3.39 \pm 0.49) - (0.336 \pm 0.024)pK_a \qquad (6)$$

Now it is possible to calculate the heats and free energies of formation of all of the species $P(OEt)_5(OH)_{5-n}$, $n = 0$–5. The values so obtained are found in Table I.

Thermodynamics of the Ethyl Esters of Phosphoric Acid. Thermodynamic data for phosphoric acid and triethyl phosphate are found in Table I. To obtain the free energy of formation of triethyl phosphate it was necessary to estimate the standard entropy in the gas phase, using the method of atomic contributions.[9] Direct calculation of the free energy of transfer from the gas phase to aqueous solution, using vapor pressure and solubility data, is not possible because of the very great solubility of the ester (5.5 M[16]). A value was estimated from the free energies of transfer of the tri-*n*-propyl and tri-*n*-butyl esters, taking advantage of the additive nature of the free

Table IV. Free Energies of Transfer of Phosphate Esters

Ester $OP(OR)_3$ R =	Solubility, M	Vapor pressure, mm (atm)	ΔG_t,[a] kcal mol^{-1} "Exptl"	 Calcd
CH_3-	∞[b]	0.94[c] (1.2×10^{-3})	"−∞"	−5.00
CH_3CH_2-	5.5[d]	0.40[c] (5.3×10^{-4})	"−5.49"	−4.38
$CH_3CH_2CH_2$-	0.029[e]	0.039[f] (5.1×10^{-5})	−3.76	
$CH_3CH_2CH_2CH_2$-	0.0016[g]	0.0061[h] (8.0×10^{-6})	−3.14	

[a] Free energy of transfer from the gas phase, standard state the ideal gas at 1 atm, to aqueous solution, standard state 1 M with an infinitely dilute reference state. "Experimental" values are calculated as $+RT \ln (p/c)$; "calculated" values are obtained by extrapolation, assuming that ΔG_t is linear in number of carbon atoms per molecule. [b] Reference 16. [c] Reference 16. [d] Reference 16. [e] Reference 58. [f] Reference 59. [g] Reference 60. [h] Reference 61.

energies of transfer.[17] The data employed are found in Table IV.

Gerlt et al.[18] have measured heats of hydrolysis for the reactions

$$EtOPO_3H^-(aq) + (H_2O(l) = EtOH(aq) + H_2PO_4^-(aq) \quad \Delta H^\circ = -1.56 \pm 0.17^{19} \quad (7)$$

$$EtOPO_3^{2-}(aq) + H_3O(l) = EtOH(aq) + HPO_4^{2-}(aq) \quad \Delta H^\circ = 0.29 \pm 0.10^{19} \quad (8)$$

$$(EtO)_2PO^-(aq) + H_2O(l) = EtOH(aq) + EtOPO_3H^-(aq) \quad \Delta H^\circ = -1.84 \pm 0.45 \quad (9)$$

To calculate the enthalpy changes for the corresponding reactions with neutral starting materials and products requires heats of ionization. For phosphoric acid values of −1.83 ± 0.04[20] and 1.00 ± 0.02[20] for the first and second heats of ionization were used. For monoethyl phosphate, the second heat of ionization is −0.80 ± 0.05.[18] For the other heats of ionization of the ethyl esters it was necessary to use values for the corresponding methyl esters. For monomethyl phosphate Bunton et al.[21] report pK_a data at a series of temperatures which led[22] to values of −4.37 ± 1.41 and −0.68 ± 0.50 for the first and second heats of ionization. For dimethyl phosphate, Bunton et al.[24] report pK_a values at three temperatures, from which an approximate value of the heat of ionization can be estimated as −3.15 ± 1.08. The desired heats of hydrolysis are then

$$EtOPO_3H_2(aq) + H_2O(l) = EtOH(aq) + H_3PO_4(aq) \quad \Delta H^\circ = -4.10 \pm 1.42 \quad (10)$$

$$(EtO)_2PO_2H_2(aq) + H_2O(l) = EtOH(aq) + EtOPO_3H_2(aq) \quad \Delta H^\circ = -0.62 \pm 1.83 \quad (11)$$

An approximate value for the heat of hydrolysis of trimethyl phosphate has been reported[25] as:

$$(MeO)_3PO(aq) + OH^-(aq) = MeOH(aq) + (MeO)_2PO_2^-(aq) \quad \Delta H^\circ \simeq -20.0 \quad (12)$$

from which may be calculated:

$$(MeO)_3PO(aq) + H_2O(l) = (MeOH)(aq) + (MeO)_2PO_2H(aq) \quad \Delta H^\circ \simeq -3.5 \quad (13)$$

This value will be used as an approximation to the value for triethyl phosphate.

For complete hydrolysis of triethyl phosphate, the enthalpies of formation in Table I lead to

$$(EtO)_3PO(aq) + 3H_2O(l) = 3EtOH(aq) + H_3PO_4(aq) \quad \Delta H^\circ = -7.29 \pm 1.35 \quad (14)$$

From the enthalpy changes for the individual hydrolytic steps (eq 10, 11, and 13) the enthalpy change for reaction 14 can be calculated as 8.22. The agreement is clearly within the combined uncertainties of the two values. One-third of ΔH° for reaction 14, or −2.56 ± 0.73, is then a reasonable estimate of the enthalpy change in reactions 10, 11, and 13.

Although one would expect some variation in ΔH for reactions 10, 11, and 13 as a consequence of the change in pK_a of the OH being formed (eq 6), this variation will be small and less than the other uncertainties in ΔH°. This average value of ΔH° was used to calculate enthalpies of formation of the mono- and diesters; see Table I.

For reaction 14, the free energy of formation data in Table I lead to a value of $\Delta G^\circ = -10.58 \pm 2.25$ kcal mol^{-1}. From this value and ΔH° for reaction 14, a value for the symmetry corrected[26] entropy change per individual ester hydrolysis step can be calculated as 2.32 ± 3.55 eu, in satisfactory agreement with the value calculated above for other ester hydrolysis reactions. Variations in ΔG° per step resulting from the pK_a variation from diethyl phosphate to monoethyl phosphate to phosphoric acid will be ignored here also, as being less than the uncertainties in the data. An average value of the symmetry corrected free energy of hydrolysis of −3.19 ± 1.31 kcal mol^{-1} per step was used to calculate free energies of formation of the individual esters; see Table I.

From the thermodynamic quantities for the phosphorane, $P(OH)_{5-n}(OEt)_n$, and phosphate $PO(OH)_{3-n}(OEt)_n$ species in Table I, the free energies and enthalpies of the water or hydroxide addition reactions may be calculated. These values are found in Table V. The error limits on these values are large, as a consequence of the lack of sufficient accurate data to define the thermodynamic values for the ethyl phosphates more clearly and also of the scarcity of data for reactions of the form of eq 3 with X = P, which would permit a more reliable estimation of $\Delta H''$ and $\Delta G''$. Nevertheless, the present results markedly lessen the uncertainties concerning the hydration equilibria for phosphate derivatives, and illustrate both the potential of this approach and the need for more fundamental thermodynamic data for phosphate esters. In order to calculate some of these values it was necessary to estimate pK_a's for the pentacovalent species; the values used are found in Table VI.

Thermodynamics of Monomeric Metaphosphate. Monomeric metaphosphate ion, PO_3^-, is accepted as an intermediate in certain phosphoryl transfer reactions.[28] It has never been isolated and no direct evidence concerning its thermodynamic properties is available. For purposes of comparison with the pentacoordinate species described above, it is of interest to consider what can be deduced concerning the stability of this tricoordinate species. Only two unambiguous facts are available concerning monomeric metaphosphate: (1) it has never been detected by any spectroscopic method in aqueous solution, and therefore is at least 2 kcal higher in free energy level than is $H_2PO_4^-$; and (2) from the free energy activation for reactions leading to metaphosphate, and the free energy for the overall hydrolysis, it may be calculated that PO_3^- is no more than 34 kcal mol^{-1} higher in free energy level than $H_2PO_4^-$. Thus, one can be certain that for the reaction

$$H_2PO_4^-(aq) = H_2O(l) + PO_3^-(aq) \quad \Delta G^\circ = 18 \pm 16$$

Table V. Enthalpies and Free Energies of Addition and Elimination Reactions of Phosphoric Acid and Its Esters

Reaction	$\Delta H°$	$\Delta G°$	$\log K$
$H_2O + H_3PO_4 \rightleftarrows P(OH)_5$	11 ± 2	17 ± 3	−12.2 ± 2.2
$H_2O + EtOPO_3H_2 \rightleftarrows EtOP(OH)_4$	9 ± 2	16 ± 3	−11.6 ± 2.4
$H_2O + (EtO)_2PO_2H \rightleftarrows (EtO)_2P(OH)_5$	8 ± 2	16 ± 3	−11.6 ± 2.0
$H_2O + (EtO)_3PO \rightleftarrows (EtO)_3P(OH)_2$	7 ± 2	14 ± 4	−10.3 ± 2.7
$H_2O + H_2PO_4^- \rightleftarrows P(OH)_4O^-$		26 ± 3	−18.6 ± 2.4
$H_2O + EtOPO_3H^- \rightleftarrows (EtO)P(OH)_3O^-$		25 ± 4	−18.0 ± 2.6
$H_2O + (EtO)_2PO_2^- \rightleftarrows (EtO)_2P(OH)_2O^-$		25 ± 3	−18.0 ± 2.2
$H_2O + HPO_4^{2-} \rightleftarrows P(OH)_3(O)_2^{2-}$		34 ± 4	−24.7 ± 2.6
$H_2O + EtOPO_3^{2-} \rightleftarrows (EtO)P(OH)_2(O)_2^{2-}$		33 ± 4	−24.0 ± 2.8
$H_2O + PO_4^{3-} \rightleftarrows P(OH)_2(O)_3^{3-}$		41 ± 4	−30.0 ± 2.8
$HO^- + (EtO)_3PO \rightleftarrows (EtO)_3P(OH)O^-$		4 ± 4	−2.8 ± 2.8
$HO^- + (EtO)_2PO_2^- \rightleftarrows (EtO)_2P(OH)(O)_2^{2-}$		22 ± 3	−16.0 ± 2.4
$HO^- + (EtO)PO_3^{2-} \rightleftarrows (EtO)P(OH)(O)_3^{3-}$		37 ± 4	−27.3 ± 3.0
$H_3PO_4 \rightleftarrows HPO_3 + H_2O$		32 ± 2	−23.1 ± 1.5
$H_2PO_4^- \rightleftarrows PO_3^- + H_2O$		27 ± 2	−19.6 ± 1.8
$HPO_4^{2-} \rightleftarrows PO_3^- + OH^-$		36 ± 2	−26.4 ± 1.8
$EtOPO_3H_2 \rightleftarrows HPO_3 + EtOH$		29 ± 2	−21.0 ± 1.8
$EtOPO_3H^- \rightleftarrows PO_3^- + EtOH$		25 ± 3	−18.1 ± 2.0
$EtOPO_3^{2-} \rightleftarrows PO_3^- + EtO^-$		37 ± 3	−27.0 ± 2.0
$(EtO)_2PO_3^- \rightleftarrows EtOPO_3 + EtO^-$		48 ± 3	−35.2 ± 2.0
$(EtO)_2PO_2H \rightleftarrows EtOPO_3 + EtOH$		28 ± 3	−20.5 ± 2.0

Table VI. pK_a's of Phosphorus Acids[a]

Acid	pK_{-1}[b]	pK_1	pK_2	pK_3
H_3PO_4	−2.3[h]	2.12[d]	7.21[d]	12.67[e]
$EtOPO_3H_2$	−2.9[e]	1.50[f]	6.58[f]	
$(EtO)_2PO_2H$	−3.5[e]	0.76[g]		
$(EtO)_3PO$	−4.1[e]			
H_5PO_5	−8.4[h]	8.5[c]	13.3[c]	18.0[c]
$EtOPO_4H_4$	−9.1[e]	7.8[e]	12.6[e]	17.3[e]
$(EtO)_2PO_3H_3$	−9.8[e]	7.2[e]	12.0[e]	16.7[e]
$(EtO)_3PO_2H_2$	−10.5[e]	6.5[e]	11.3[e]	
$(EtO)_PO_2H$	−11.2[e]	5.8[e]		
$(EtO)_5P$	−11.9[e]			
HPO_3		−1.43[i]		
$pNPOPO_3H_2$[j]		0.21[k]	5.18[k]	
$DNPOPO_3H_2$[l]		−0.5[m]	4.5[n]	

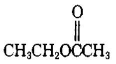
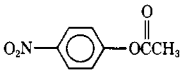
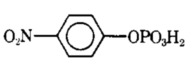
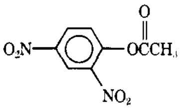
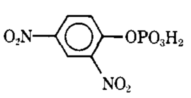
[a] In water at 25 °C. [b] pK_a for ionization of the cationic conjugate acid. [c] Calculated by the method of Branch and Calvin: ref. 13. [d] Reference 16. [e] Calculated using a pK_a increment of 0.66 for each ethoxy group replacing a hydroxy group. This increment is the average of the values found for orthophosphate mono- and diesters. [f] Assumed to be the same as for the methyl ester: ref 21. [g] Assumed to be the same as for the methyl ester: ref 24. [h] Calculated by a modification of the method of Branch and Calvin,[13] using log K_a of H_3O^+ (−2) as starting point instead of log K_a of H_2O (16). [i] Assumed to be equal to the pK_a for nitric acid: ref 62. [j] Mono-*p*-nitrophenyl phosphate. [k] Reference 63. [l] Mono-2,4-dinitrophenyl phosphate. [m] Estimated from pK_1 for *p*-nitrophenyl phosphate, assuming that the effect of the second nitro group on pK_1 is the same as on pK_2. [n] Reference 64.

Some less unambiguous information allows the free energy difference to be specified more closely, with high probability, though less certainty.

The kinetics of hydrolysis of acetyl phosphate dianion may show a common ion effect,[29] although the rate retardation, if any, is very small and only observable at high ionic strength. At high concentrations of acetyl phosphate, particularly when the ionic strength is made very high using an inert salt, pyrophosphate becomes a significant product, showing that metaphosphate can be trapped by inorganic phosphate, in the presence of water.[29] Phosphate trapping is more effective at pH 9.7 than at 5.6, so that it is presumably water which is the effective nucleophile at pH 5.6 and not hydroxide.[29] These observations require that the second-order rate constants for acetate, phosphate, and water be of comparable magnitude, i.e., that the metaphosphate intermediate shows very little selectivity. Toward unreactive electrophiles there is ordinarily a considerable difference in nucleophilicity between water, acetate, and phosphate: for *p*-nitrophenyl acetate, for example, the rate constants are ca. 10^{-6}, 10^{-3}, and 10^{-2} M^{-1} min^{-1}, respectively.[30] This reactivity difference may be expressed in terms of Ritchie's N_+ values, which may be estimated as 0, 3.4, and 4.1,[31] respectively.

Low selectivity is commonly observed when the reactions have become so fast that the diffusion-controlled limit on rate constants is being reached.[32] Furthermore, it has been observed that the rates of nucleophilic substitution reactions of amines with nitrophenyl phosphate dianions are very insensitive to the pK_a of the amine, even though the rate of disappearance of the starting material is markedly accelerated by the amine. These various observations may be quantitatively reconciled by a mechanism for the reaction involving preequilibrium formation of a metaphosphate-leaving group "encounter complex", followed by rate-limiting capture of the metaphosphate by solvent or external nucleophile. The encounter complex is analogous to an intimate ion pair, in that there is no intervening solvent, but in the present case both species may be anions. The "encounter complex" from acetyl phosphate or a nitrophenyl phosphate is far more likely to revert to starting materials than to react with solvent, because the leaving group is a better nucleophile, whether measured by pK_a, N_+, or whatever, although there is no measure of nucleophilicity within an encounter complex. Since the reaction of the leaving group with metaphosphate is within an encounter complex, it will be faster than the diffusion-controlled limit. It is difficult to estimate the rate of the reaction of solvent with the metaphosphate ion. Fortunately, the rate of this reaction can be calculated from the results with nitrophenyl phosphate dianions. For the reactions of amines with nitrophenyl phosphate dianion we assume that the rate-determining step is the diffusion-controlled reaction of the amine with the metaphosphate-phenolate "encounter complex". The rate constant for this process is assumed to be 10^{10} M^{-1} s^{-1} for all amines.[33] Then for *p*-nitrophenyl phosphate dianion, from the observed second-order rate constant of 2.4×10^{-8} M^{-1} s^{-1} (for the reaction with pyridine, corrected to 25 °C from the value at 39 °C using the published $\Delta H^{\ddagger}$ for hydrolysis of the dianion) one can calculate

Table VII. Standard Free Energies of Hydrolysis for Aryl Phosphates[a]

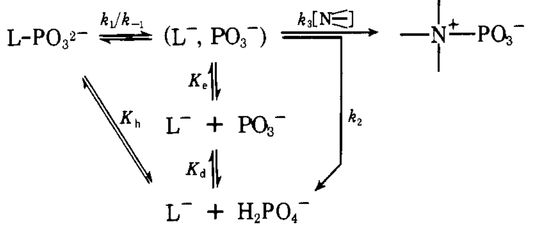
Acetate ester	$\Delta G^\circ_{\text{hydrol}}$[b]	Phosphate ester	$\Delta G^\circ_{\text{hydrol}}$[b]
 $CH_3CH_2O\overset{O}{\overset{\|}{C}}CH_3$	-1.66[c]	$CH_3CH_2OPO_3H_2$	-2.87[d]
	-9.43[e]		-10.64[d]
	-12.37[f]		-13.58[d]

[a] In water at 25 °C. Standard states are 1 M solutions with an infinitely dilute reference state except for water, for which the standard state is the pure liquid. All equilibria are expressed in terms of the neutral, un-ionized reactants and products. [b] In kcal mol^{-1}. [c] Reference 50. [d] Calculated as described in the text. [e] Reference 65. [f] Estimated from the correlation between log K_{hydrol} of ROAc and the pK_a of ROH: ref 65.

a dimensionless equilibrium constant for formation of the "encounter complex" from the ester dianion of 2.4 × 10^{-18}. From this equilibrium constant and the overall rate constant for the solvolysis of the dianion at 25 °C of 1.35 × 10^{-9} s^{-1}, the rate of reaction of solvent water with the encounter complex is 5.8 × 10^8 s^{-1}. A similar argument for dinitrophenyl phosphate leads to a rate constant for reaction of water with metaphosphate of 1.4 × 10^9 s^{-1}. Considering the uncertainties in the treatment the agreement that the rate of this reaction is 10^9 s^{-1} is very encouraging. This value can now be used with all of the other reactions which have been assigned the metaphosphate mechanism. This calculation leads to values of the equilibrium constant for formation of metaphosphate from phosphate. It is first necessary to calculate equilibrium constants for hydrolysis of these esters; we make the assumption that the ratio of equilbrium constants for ester formation from two alcohols with phosphate will be the same as the ratio of the corresponding equilibrium constants with acetate. In this way the equilibrium constants in Table VII were calculated.

In order to obtain the free energy of free metaphosphate ion, it is also necessary to estimate the equilibrium constant for formation of the encounter complex from metaphosphate and leaving group; we will use the value suggested by Hine for formation of encounter complexes, namely $K_e = 0.017$ M^{-1}.[34] The model used to calculate the free energy of dehydration of phosphate is then given in Scheme I, where L$^-$ is the leaving group, (L$^-$, PO_3^-) is the encounter complex, K_e is the equilibrium constant for formation of the encounter complex from the separate ions, and K_d is the equilibrium constant for dehydration of $H_2PO_4^-$.

Scheme I



Since K_h and K_e are known, and $k_{obsd} = k_1k_2/k_{-1}$ (or k_1k_3/k_{-1}) with k_2 (or k_3) known, K_d can be calculated. An essential requirement for this approach to work is that $k_{-1} \gg k_2$; this will be true for leaving groups more basic than water. When the leaving group is methanol, $k_{-1} \approx k_2$, and there will be an error of ca. twofold in k_2/k_{-1}, which is tolerable for approximate calculations such as these. When the leaving group is a neutral phenol or acetic acid, then we would expect $k_{-1} < k_2$, and the treatment should break down.

For an encounter complex involving two anions, K_e should be less favorable, as a result of electrostatic repulsion, than for an encounter complex involving an anion and a neutral molecule. The magnitude of this repulsion is difficult to estimate, but in aqueous solution it should be small, perhaps 1 kcal mol^{-1}. When the calculations are carried out (see Table VIII) for reactions of dianions and methylphosphate monoanion, the average value for the ΔG_d, free energy of dehydration of orthophosphate monoanion to monomeric metaphosphate ion, is 26.6 ± 0.7. The only value which deviates seriously is that from methylphosphate monoanion, which is 1.3 kcal lower, about as one would expect from the electrostatic effect. Of the monoanion reactions, only that of 2,4-dinitrophenyl phosphate monoanion leads to a value of ΔG_d deviating seriously from the average. The higher value is consistent with k_1 being rate determining and not k_2 as was assumed. Reactions of phosphate monoester monoanions leading to monomeric metaphosphate are assumed to go by way of zwitterions, which would also go by the immediate products of the k_{-1} step. Approximate estimation of pK_a values suggests that only for 2,4-dinitrophenyl phosphate would the zwitterion be higher energy than metaphosphate plus phenol, and thus only for this case should there be a higher barrier for the k_{-1} step. For acetylphosphate monoanion there is a lower activation energy path involving cyclic proton transfer, which makes k_{-1} (and k_1) faster than would be expected from the pK_a of the leaving group; consequently acetyl phosphate monoanion has k_2 as rate-determining step.

The overall agreement in ΔG_d values is remarkably good, considering the range in numerical magnitude of the rate constants from which they are deduced, and the extrapolations required in some cases. Thus we conclude that the thermodynamics of metaphosphate anion can be deduced with fair confidence.

In order to calculate the free energy of formation of metaphosphoric acid itself, it is necessary to estimate the pK_a of the acid; it will be assumed that this is equal to the pK_a for nitric acid; see Table VI. Ordinarily inorganic acids differing only in the nature of the central atom and not in structure or charge type have very similar pK_a's. It will be of interest to calculate free energies for formation of esters of metaphosphoric acid; these will necessarily be imprecise, but should be at least qualitatively useful; it will be assumed that the equilibrium constant for formation of a metaphosphate ester is the same as the equilibrium constant for formation of the corresponding orthophosphate monoester. The correlation of free energy of reaction 5 with pK_a cannot be used here, because the pK_a of metaphosphate is likely to be influenced by resonance involving pπ-pπ double bonds of a sort not present in the orthophosphates or phosphoranes. In this way were calculated the free energy of formation values found in Table I and the free energy of elimination values found in Table V.

pH Rate Profiles. In Table IX are presented rate constants for hydrolysis of mono-, di-, and trimethyl phosphates, by the bimolecular paths (P-O and C-O cleavage) and the unimolecular path (metaphosphate). For those paths which are kinetically undetectable, rate constants were estimated as follows: For bimolecular attack at phosphorus, rate constants were estimated by analogy with measurable reactions, using, where necessary, electrostatic factors determined for attack at phosphorus. For bimolecular attack at carbon, it was assumed that the effect of an added negative charge upon leaving group properties was the same for phosphate as for sulfate. This effect was determined as the ratio of rates for methylsulfate monoanion or sulfate dianion as leaving groups, calculated from the Swain-Lohmann leaving group constants and the reaction constants for OH$^-$ + CH_3X and H_2O + CH_3X.[35] For uni-

Table VIII. Free Energy Change for the Dehydration of Orthophosphate Monoanion to Monomeric Metaphosphate Anion[a]

Reactant	k_{obsd}, s^{-1}	$\Delta G_{overall}$,[b] kcal mol^{-1}	ΔG_d, kcal mol^{-1}
$AcOPO_3^{2-}$	9.36×10^{-6} [c]	−9.91 [d]	26.7
$AcOPO_3H^-$	3.3×10^{-5} [c]	−10.78 [d]	26.8
$CH_3OPO_3H^-$	1.6×10^{-10} [e]	−2.03 [f]	25.3
pNPOPO$_3^{2-}$ [g]	1.35×10^{-9} [h]	−5.34 [i]	27.3
pNPOPO$_3$H$^-$ [g]	1.56×10^{-7} [h]	−8.02 [i]	27.2
DNPOPO$_3^{2-}$ [j]	3.0×10^{-5} [k]	−10.58 [i]	26.6
DNPOPO$_3$H$^-$ [j]	8.0×10^{-7} [k]	−9.99 [i]	28.2 [o]
pNPOPO$_3^{2-}$ [l] + amines	2.4×10^{-8} [h]	−5.34 [i,m]	27.0
DNPOPO$_3^{2-}$ [l] + amines	1.8×10^{-4} [n]	−10.58 [i,m]	26.9
			Av 27 ± 1

[a] In water at 25 °C. [b] Free energy changes for the hydrolysis of the reactant, giving products with the same total charge. [c] Reference 29. [d] Reference 65. [e] Reference 21. [f] Calculated from the free energy of formation data in Table I and the pK_a values in Table VI. [g] Mono-p-nitrophenyl phosphate. [h] Reference 66. [i] Estimated as described in the text. [j] Mono-2,4-dinitrophenyl phosphate. [k] Reference 67. [l] Bimolecular reaction of amines with the phosphate ester: the rate constant for pyridine is used (M^{-1} s^{-1}). [m] The free energy of the *hydrolysis* is used to relate the free energy levels of metaphosphate and orthophosphate; see text. [n] Reference 68. [o] Not included in the average.

Table IX. Rate Constants for Hydrolysis of Phosphate Esters[a]

Reactants	Bimolecular attack at P	Bimolecular attack at C	Unimolecular
$(CH_3O)_3PO$, H_3O^+	(2.1×10^{-11}) [b]	(5.5×10^{-11}) [c]	
$(CH_3O)_3PO$, (H_2O)	(1×10^{-10}) [d]	2×10^{-8} [e]	
$(CH_3O)_3PO$, OH^-	1.6×10^{-4} [e]	(1.1×10^{-6}) [f]	
$(CH_3O)_2PO_2H$, H_3O^+	2.1×10^{-11} [g]	1.8×10^{-10} [g]	
$(CH_3O)_2PO_2H$, (H_2O)	1.2×10^{-10} [h]	4.6×10^{-10} [h]	(1×10^{-14}) [i]
$(CH_3O)_2PO_2^-$, (H_2O)	2×10^{-14} [j]	(1.0×10^{-16}) [k]	(2×10^{-29}) [l]
$(CH_3O)_2PO_2^-$, OH^-	6.8×10^{-12} [m]	2.7×10^{-11} [m]	
$CH_3OPO_3H_2$, H_3O^+	1.2×10^{-10} [n]	3.3×10^{-10} [n]	
$CH_3OPO_3H_2$, (H_2O)	1.6×10^{-10} [o]	8.8×10^{-11} [p]	(1×10^{-14}) [i]
$CH_3OPO_3H^-$, (H_2O)	(2.6×10^{-14}) [q]	(1.9×10^{-17}) [k]	2.6×10^{-10} [r]
$CH_3OPO_3^{2-}$, (H_2O)	(4.1×10^{-18}) [s]	(4.3×10^{-24}) [t]	(1×10^{-20}) [l]
$CH_3OPO_3^{2-}$, OH^-	(2.9×10^{-19}) [u]	(6.7×10^{-16}) [t]	

[a] In aqueous solution at 25 °C. Values in parentheses are estimated. Other values are measured rate constants, or obtained by extrapolation from data at higher temperatures (M^{-1} s^{-1}, H_3O^+, OH^-; s^{-1}, H_2O). [b] Estimated assuming that the rate constant has the same numerical magnitude as that for the dimethyl ester. [c] Estimated assuming that the rate constant per methyl will be equal to the rate constant per methyl observed for the dimethyl ester, decreased by the ratio of the rate constants per methyl observed for the dimethyl and monoethyl esters. [d] Estimated, assuming that the rate constant will have the same numerical magnitude as the corresponding rate constants for the mono and dimethyl esters. [e] Reference 68. [f] Calculated from the rate constant for the analogous reaction for the dimethyl ester monoanion, using the Swain-Lohman leaving group parameters.[35] [g] Calculated from data in ref 24, using the activation energy (for the monomethyl ester) from ref 69, and assuming that the percentage of PO cleavage[24] was the same at 25 °C as at 100 °C. [h] Calculated from data, including overall activation energies and percentage of PO cleavage, from ref 24. [i] Estimated from free energy of formation data in Table I, as described in the text. [j] Calculated from a value at 100 °C[24] assuming that $\Delta S^{\ddagger}$ was the same as for the reaction of H_2O with neutral dimethyl phosphate. [k] Estimated from the rate constant for the analogous reaction for the neutral ester, using the Swain–Lohman leaving group parameters.[35] [l] Estimated from free energy of formation data in Table I, and the pK_a values for dimethyl phosphate (Table VI) and methanol,[70] as described in the text. [m] Calculated from the rate constants at 115 and 125 °C[71] and the percentage of CO cleavage at 140 °C.[24] [n] Calculated from rate constants at 100 °C[21] and activation energies,[69] assuming that the percentage of PO cleavage [21] is the same at 25 °C as it is at 100 °C. [o] Calculated from the rate constant at 100 °C,[21] assuming that the activation energy is the same as for the analogous reaction of the dimethyl ester.[24] [p] The rate constant at 100 °C was calculated from the observed pseudo-first-order rate constant at pH 1, by subtracting the contributions of the acid-catalyzed reaction, the monoanion reaction, and the water reaction involving attack at carbon. The residual rate constant, 1.1×10^{-6} s^{-1}, is taken as the rate constant for reaction with PO cleavage, and is very similar to the value observed for dimethyl phosphate. [q] Estimated from the rate constant for the analogous reaction of neutral monomethyl phosphate, assuming that the rate ratio for neutral/monoanion will equal that observed for the dimethyl ester. [r] Calculated from rate constants at higher temperatures, and a measured activation energy.[21] [s] Estimated from the analogous rate constant for the monoanion, assuming that the ratio of the rate constants for the dianion and monoanion will be the same as the ratio for monoanion and neutral. [t] Estimated from the analogous rate constant for dimethyl phosphate monoanion, using the Swain-Lohman leaving group parameters. [u] Estimated from the analogous rate constant for the monoanion of dimethyl phosphate, assuming that the ratio of rate constants for monomethyl phosphate dianion and dimethyl phosphate monoanion will be the same as that for dimethyl phosphate monoanion and neutral trimethyl phosphate.

molecular decomposition by way of a metaphosphate intermediate, rate constants were calculated by taking the equilibrium constant for formation of the "encounter complex", and multiplying this by the rate constant for capture of metaphosphate by water, i.e., 10^9 s^{-1}.

Figure 2 shows the pH-rate profiles derived from these rate constants. Lines for each mechanistic class are drawn in to show the mechanistic complexity of phosphate ester hydrolyses, which can have repeated changes in relative rates for the different paths as the pH is changed.

Part of the value of having the complete pH-rate profiles for phosphate ester hydrolyses, including the unobservable portions, is in the interpretation of enzymic rate enhancements. This is particularly the case for monoalkyl phosphates, for

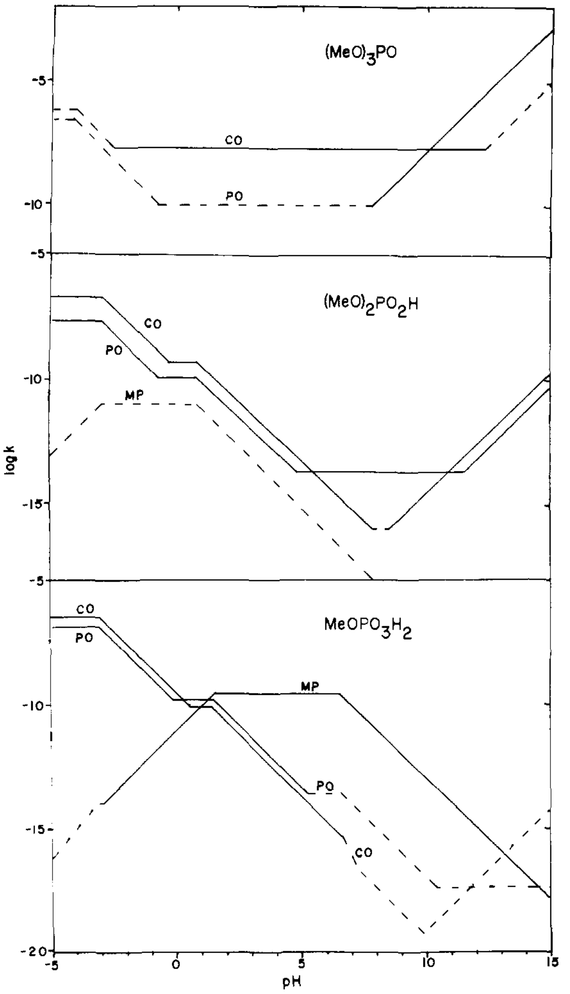


Figure 2. pH-rate profiles for mono-, di-, and trimethyl phosphates in water at 25 °C: solid lines, calculated using rate constants calculated from experimental values; dashed lines, calculated using rate constants estimated in this work; CO, hydrolysis with C–O bond fission; PO, hydrolysis with P–O bond fission and bimolecular attack at phosphorus to give a phosphorane intermediate; MP, hydrolysis with unimolecular bond cleavage to give a monomeric metaphosphate intermediate.

which the major route for nonenzymic hydrolysis is breakdown to metaphosphate. This work suggests that enzymic reactions probably do not involve metaphosphate, since the interpretation of metaphosphate kinetics presented above requires that metaphosphate formation is already occurring at a rate principally limited by the equilibrium free energy change, so that little rate enhancement is possible.[36a]

Kinetic data for the alkaline phosphatase catalyzed hydrolysis of methyl phosphate have recently been reported; for this ester k_{cat}/Km, which is equivalent to the second-order rate constant for reactions of substrate with free enzyme, is 5.7×10^3 M^{-1} s^{-1} at pH 8, 25 °C.[36b] At this pH the rate constant for uncatalyzed water attack at phosphorus is ca. 10^{-15} s^{-1}. This can be converted to the second-order rate constant, ca. 10^{-17} M^{-1} s^{-1} for comparison of enzyme and water as nucleophiles. By this comparison, the enzymic reaction is 10^{21} faster. If the comparison is between k_{cat} and the first-order rate constant for the uncatalyzed reaction, then the enzymic rate enhancement is 10^{17}.

Figure 3 shows a reaction coordinate diagram for the hydrolysis, with P–O clearage, of monomethyl phosphate monoanion at 25 °C. This figure permits comparison of the addition and elimination modes of phosphate monoester hydrolysis. (Here, and throughout the remainder of this paper, equilibrium constants for addition to analogous methyl and ethyl esters are assumed to be the same. This will not be exactly correct, but the error is small relative to the uncertainty in the equilibrium constants.) The intermediates are at very similar free energy levels relative to the starting material, and the metaphosphate path is preferred simply as a result of its lower activation barrier. This difference in activation barrier is rationalizable in terms of the amount of nuclear motion required for the two processes, since an additional heavy atom, with substituents or solvation, must move a significant distance for the tetracoordinate to pentacoordinate transformation, as opposed to the tetracoordinate to tricoordinate transformation.

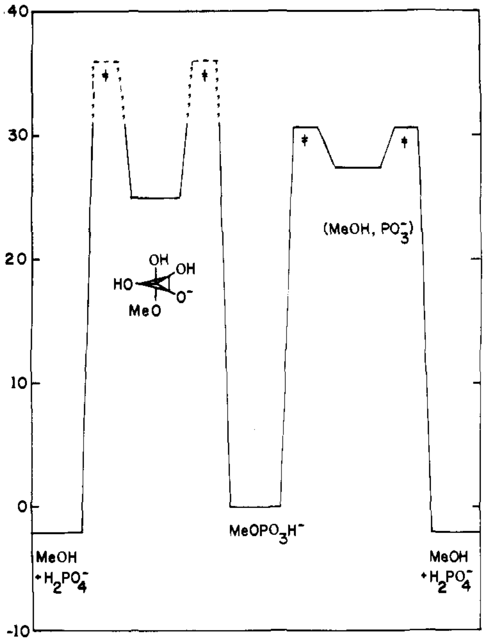


Figure 3. Reaction coordinate diagram for the hydrolysis of monomethylphosphate monoanion. Free energies of activation are expected to be very similar for the formation and breakdown processes for both mechanisms.

At this point one should also address the problem of the nonexchange into trimethyl phosphate when it reacts with H^{18}O$^-$.[68] Given the very similar leaving group properties of OH$^-$ and OCH$_3^-$, and the high barrier to loss of either deduced above, this lack of exchange is at first sight quite surprising. It has in fact been used to argue for a direct displacement mechanism. The situation is somewhat more complicated than it initially appears. Since leaving groups must be axial,[14] exchange of ^{18}O into the starting material requires pseudorotation of the intermediate. Since O$^-$ is far less electronegative than OR, it must have a strong preference for an equatorial position, so that pseudorotation requires protonation of the O$^-$ before (or possibly as) it pseudorotates.

The neutral intermediate is 10 kcal less stable than the anionic species in 1 M NaOH, so that the barrier to pseudorotation need only be greater than 9 kcal mol^{-1} to make exchange an unfavorable process. Benkovic has recently reviewed the available information on pseudorotation rates, and has concluded that the free energy barrier is between 5 and 15 kcal mol^{-1}.[18] Thus the nonobservance of exchange does not necessarily rule out a pentacovalent intermediate. It should be noted that a stepwise protonation–pseudorotation–deprotonation mechanism for exchange implies that exchange accompanying alkaline hydrolysis would become observable at lower pH.

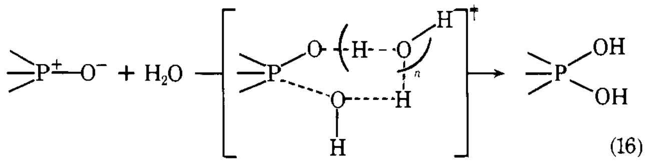
Rate Equilibrium Correlations. A useful perspective of the nature of the difference between phosphate and acyl transfer reactions is gained by considering these reactions from the viewpoint of Marcus' theory for rate processes.[37] Starting with the simplest equation used by Marcus (eq 1, ref 37a), but expressing it in terms of rate and equilibrium constants, gives

$$\log k = 10 - b(1 - \log K/4b)^2 \qquad (15)$$

where b is the log k equivalent[34] of the Marcus intrinsic barrier Λ.[37b] The collision rate for species in aqueous solution is taken as 10^{10} M^{-1} s^{-1}.[33,34] Equation 15 holds for $|\log K| \leq 4b$; outside these limits log k values will fall on the limiting lines of slope 0 or 1. For this approach to be applied, the rate and equilibrium constants must refer to a single elementary reaction step.

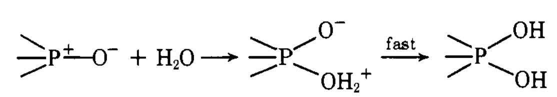
Figure 4 shows a graph of log k vs. log K for the hydration of phosphate esters. For the acid-catalyzed reactions, rate constants were calculated for attack of water on the conjugate acid of the substrate, using pK_a's from Table VI. These reactions are assumed to lead initially to the cationic form of the intermediate, which then loses a proton in a fast step. However, it is also possible that the reaction proceeds by a more complex path with general-base-catalyzed (water as general base) removal of a proton from the water molecule, which attacks the protonated ester, leading to neutral phosphorane and hydronium ion. Since the pK_a of the attacking water molecule changes from 15.74 to a value between −9 and −10 as the attack proceeds, this process would be permitted by Jencks' "libido rule",[38] and seems intuitively reasonable, although there is no evidence to require this more elaborate mechanism. Figure 4 shows that both mechanisms are consistent with the data: the first imples $b \leq 4$, the second implies $b = 13$. A decision between the two possibilities could be made if data corresponding to markedly different equilibrium constants were available, as might be the case for esters of alcohols with electron withdrawing substituents. The first mechanism requires that log k, log K points fall on the limiting line of unit slope, whereas the second mechanism requires an apparent slope of 0.56; thus the mechanisms would be readily distinguished if a few points corresponding to log K's differing by ca. ten log units were available.

For the water reaction, the equilibrium constants are calculated for the process leading by a concerted, cyclic proton transfer mechanism (eq 16), to a neutral adduct, rather than



(16)

for the simpler process (eq 17) leading initially to a zwitterion.



(17)

A crude estimate of the zwitterion content of a phosphorane (based on pK_a's calculated by the method of Branch and Calvin[13]) leads to a value of one part in 10^{12}, which is relatively insensitive to the overall state of ionization of the phosphorane. The hydration of dimethyl phosphate monoanion proceeds 10^6 too rapidly for the zwitterion mechanism to be valid. This seems too great a discrepancy even for the imprecise equilibrium constants evaluated in this work, so that the concerted proton-transfer mechanism 16 is preferred. The hydroxide ion reaction is considered to be a simple addition to give the corresponding anionic phosphorane.

As is shown by Figure 4, the data can be fitted to eq 15, with $b = 13$ for hydroxide addition, and $b = 14$ for uncatalyzed water addition. It should be noted that the points for hydroxide and water addition should not be regarded as defining the *same* line, since the rate constants have different dimensions and refer to different mechanisms.

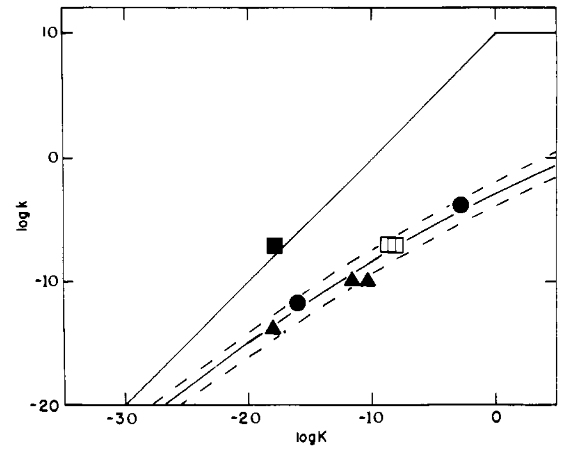


Figure 4. Rate–equilibrium correlation for reactions proceeding by way of phosphorane intermediates: (●) hydroxide-catalyzed reaction; (■) acid-catalyzed reaction, leading to cationic intermediate; (□) acid-catalzed reaction, leading to neutral intermediate plus hydronium ion; (▲) water reaction. The solid line was calculated using eq 15, with $b = 13$; the dashed lines were calculated with $b = 12$ or 14.

The intrinsic barrier for hydroxide addition to phosphate esters ($b = 12$) is much greater than that reported by Hine[34] for addition to carbonyl compounds ($b = 6.7$). Thus the inherently slow hydrolysis of posphate esters (relative to carboxylate esters) may be expressed in terms of Marcus theory as a five-order of magnitude greater intrinsic barrier to addition of hydroxide.

The rate constants estimated above for unobservable reactions involving attack on phosphorus fall satisfactorily close to the correlation lines established by the observable reactions. A more thorough test of the correlations reported in this paper would require rate and equilibrium data falling on different parts of the curve; these might be obtainable for compounds with more electron withdrawing alkoxy groups.

Experimental Section

Materials. Trimethyl phosphate, triethyl phosphate, trimethyl orthoformate, triethyl orthoformate, dimethoxymethane, diethoxymethane, tetramethyl orthocarbonate, methyl formate, ethyl formate, and propylene carbonate were reagent grade chemicals, used without further purification. Purity was checked by NMR analysis. Tetraethyl orthocarbonate was prepared by the "Organic Syntheses" procedure:[39] bp 158 °C (lit.[39] bp 158–161 °C).

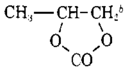
Pentaethoxyphosphorane. Following the procedure of Denney et al.[5c] 14 g of redistilled triethyl phosphite was allowed to react with 10.5 g of freshly prepared diethyl peroxide. Workup was as described,[5c] but the phosphorane was extracted three times with propylene carbonate: NMR (100 MHz) $CDCl_3$, $\delta(Me_4Si)$ 1.16 (d, $J_{PH} = 2$ Hz, of t, $J_{HH} = 7$ Hz, $P(OCH_2CH_3)_5$), 1.33 (d, $J_{PH} = 1$ Hz of t, $J_{HH} = 7$ Hz, $PO(OCH_2CH_3)_3$), 1.96 (d, $J = 6$ Hz, $\mathit{CH}_3CHOCOOCH_2$). The methyl signals were in the ratio: $P(OEt)_5/PO(OEt)_3$/propylene carbonate 1:0.11:0.04. Converted to a weight percent basis this corresponds to 88.8:4.0:7.1%, respectively.

The phosphorane was slow to dissolve in water, and apparently reacted as it dissolved; an NMR spectrum taken immediately after the phosphorane dissolved in D_2O showed only peaks attributable to triethyl phosphate and ethanol (with weak signals from the trace of propylene carbonate present in the phosphorane): NMR (100 MHz), D_2O (DSS) 1.16 (t, $J = 7$ Hz, $HOCH_2\mathit{CH}_3$), 1.82 (d, $J_{PH} = 1$ Hz of t, $J_{HH} = 7$ Hz, $PO(OCH_2\mathit{CH}_3)_3$), 1.94 (d, $J = 6$ Hz, $CH_3-CHOCOOCH$), 3.61 (q, $J = 7$ Hz, $HOCH_2CH_3$), 4.13 (approximate quintet-really two overlapping quartets, $J_{PH} \simeq J_{HH} = 7$ Hz, $PO(OCH_2CH_3)_3$). The areas of the quintet (δ 4.13) and the quartet (δ 3.61) were in the ratio of 3.00:2.00.

Calorimetry. A simple Dewar type calorimeter was used, as described previously.[40] The phosphorane did not dissolve at once, but reaction was complete within 2 min as judged by the absence of droplets of organic liquid, and linear temperature–time plots. Heats of solution of triethyl phosphate and propylene carbonate were de-

Table **X.** Heats of Solution and Reaction

(a) Heats of Solution[a]

Compd	ΔH_{soln}
$(CH_3O)_2CH_2$[c]	−3.20 ± 0.53
$(CH_3CH_2O)_2CH_2$[c]	−4.18 ± 0.32
$(CH_3O)_4C$[c]	−3.71 ± 0.44
$(CH_3CH_2O)_4C$[c]	≃−6 ± 2
H-$COOCH_3$[d]	−0.85 ± 0.05
H-$COOCH_2CH_3$[d]	−1.64 ± 0.34
 [b]	0.42 ± 0.05

(b) Heats of Reaction[a,e]

Compd	w	q_{obsd}	q_{corr}	$-\Delta H_{rxn}$
$P(OCH_2CH_3)_5$	0.986	62.3_8	61.5_3	17.99
	0.990	60.0_5	59.1_4	17.24
	0.969	61.4_5	60.5_8	19.03
				17.75 ± 0.45

[a] In water at 25 °C. [b] 0.1 N HCl. [c] 0.1 N NaOH. [d] 0.01 N HCl. [e] Liquid phosphorane reacting with 0.1 N aqueous HCl.

termined in order to correct for the presence of these impurities in the phosphorane. The results are collected in Table X, and lead to a value of −17.75 ± 0.45 kcal mol^{-1} for the enthalpy of hydrolysis of the phosphorane.

Solubility Measurements. Several milliliters of 0.1 N NaOH was placed in a test tube equipped with a joint. Excess orthoester (tetramethyl or tetraethyl orthocarbonate) was added, and the tube was stoppered and sealed with parafilm. The tube was shaken repeatedly and kept in a bath thermostated at 25 °C between shakings. Finally the layers were allowed to separate and samples of the aqueous layer were removed for NMR analysis. Concentrations were determined by electronic integration. The solubilities were: tetramethyl orthocarbonate, 1.17 M; tetraethyl orthocarbonate, 0.017 M. Vapor pressures at 25 °C were estimated from the boiling points, using estimated[72] heats of vaporization and an average heat capacity of vaporization[73] as: tetramethyl orthocarbonate, 23 Torr; tetraethyl orthocarbonate, 3.2 Torr. Then the free energies of transfer could be calculated as: tetramethyl orthocarbonate, −2.15 kcal mol^{-1}; tetraethyl orthocarbonate, −0.84 kcal mol^{-1}.

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$$\ln K = -\frac{\theta \Delta G^\circ}{R\theta} - \frac{\theta \Delta H^\circ}{R}\left[\frac{1}{\theta} - \frac{1}{T}\right] + \frac{\Delta C_{p\theta}}{R}\left[\frac{\theta}{T} - 1 + \ln\frac{T}{\theta}\right]$$

by nonlinear least squares,[23] using a suitable computer program. (b) E. C. W. Clarke and D. N. Glew, *Trans. Faraday Soc.*, **62**, 539 (1966).

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Poly(tertiary phosphines and arsines). 15. Some Polyphosphines with Terminal Dialkylamino and Alkoxy Groups[1]

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Abstract: Reactions of $[(CH_3)_3N]_2PCl$ and $(C_2M_5)_2NPCl_2$ with vinylmagnesium bromide followed by hydrolysis with aqueous alkaline tetrasodium ethylenediamine tetraacetate give the vinylphosphorus derivatives $[(CH_3)_2N]_2PCH=CH_2$ and $(C_2H_5)_2NP(CH=CH_2)_2$, respectively. The additions of the secondary phosphines R_2PH ($R = CH_3$ and C_6H_5) to $[(CH_3)_2N]_2PCH=CH_2$ catalyzed by KH give the corresponding diphosphines $R_2PCH_2CH_2P[N(CH_3)_2]_2$. The base-catalyzed additions of the primary phosphines RPH_2 ($R = CH_3$ and C_6H_5) to $[(CH_3)_2N]_2PCH=CH_2$ can be controlled to give either 1:1 adduct diphosphines $RP(H)CH_2CH_2P[N(CH_3)_2]_2$ or the 1:2 adduct triphosphines $RP[CH_2CH_2P[N(CH_3)_2]_2]_2$. Reaction of KPH_2 with $[(CH_3)_2N]_2PCH=CH_2$ followed by hydrolysis gives the tripod tetraphosphine $P[CH_2CH_2P[N(CH_3)_2]_2]_3$. Base-catalyzed additions of the secondary phosphines R_2PH ($R = CH_3$ and C_6H_5) to $(C_2H_5)_2NP(CH=CH_2)_2$ can be controlled to give either the 1:1 adducts $(C_2H_5)_2NP(CH=CH_2)CH_2CH_2PR_2$ or the 2:1 adducts $(C_2H_5)_2NP(CH_2CH_2PR_2)_2$. Base-catalyzed addition of the primary phosphines RPH_2 ($R = C_6H_5$, $CH_2C_6H_5$, and $CH_2(C(CH_3)_3)_2$) to $(C_2H_5)_2NP(CH=CH_2)_2$ gives the corresponding 1,4-diphosphacyclohexane derivatives $(C_2H_5)_2NP(CH_2CH_2)_2PR$. Methanolysis of $[(CH_3)_2N]_2PCH=CH_2$ in boiling methanol gives $(CH_3O)_2PCH=CH_2$. Potassium hydride catalyzed additions of $(C_6H_5)_2PH$ and $C_6H_5PH_2$ to $(CH_3O)_2PCH=CH_2$ give the diphosphine $(C_6H_5)_2PCH_2CH_2P(OCH_3)_2$ and the triphosphine $C_6H_5P[CH_2CH_2P(OCH_3)_2]_2$, respectively. The phosphines with terminal methoxy groups $R_2PCH_2CH_2P(OCH_3)_2$, $RP[CH_2CH_2P(OCH_3)_2]_2$ ($R = CH_3$ and C_6H_5), and $P[CH_2CH_2P(OCH_3)_2]_3$ can be obtained by methanolysis in boiling toluene of the corresponding phosphines with terminal dimethylamino groups. The base-catalyzed addition of $C_6H_5P(H)CH_2CH_2P[N(CH_3)_2]_2$ to $(CH_3O)_2PCH=CH_2$ gives $C_6H_5P[CH_2CH_2P(OCH_3)_2][CH_2CH_2P[N(CH_3)_2]_2]$. The proton, phosphorus-31, and carbon-13 NMR spectra of these new organophosphorus derivatives are described.

Previous papers of this series describe the preparation of poly(tertiary phosphines) in which the phosphorus atoms are linked by $-CH_2CH_2-$ bridges and the terminal positions on each phosphorus atom are occupied by hydrocarbon groups such as phenyl,[3] methyl,[4] or neopentyl[5] bonded to the phosphorus atoms through phosphorus-carbon bonds. We have also reported several polyphosphines containing terminal hydrogen atoms bonded to the trivalent phosphorus atoms through phosphorus-hydrogen bonds.[6] Related poly(tertiary phosphines) containing PCH_2CH_2P structural units have also been studied by other research groups.[7-9]

This paper describes the first polyphosphines containing PCH_2CH_2P structural units and dialkylamino or alkoxy terminal groups bonded to the trivalent phosphorus atoms through phosphorus-nitrogen and phosphorus-oxygen bonds, respectively. The polyphosphines containing terminal methoxy groups provide chelating ligands with stronger π-accepting properties than the previously available polyphosphines,[3-5] in which only carbon atoms are bonded to phosphorus. Furthermore, the relative susceptibilities of phosphorus-nitrogen and phosphorus-oxygen bonds toward cleavage under conditions where phosphorus-carbon bonds are stable suggests that the new polyphosphines described in this paper may be useful as intermediates for the preparation of a variety of potentially useful ligands in which various types of terminal groups are bonded to the trivalent phosphorus atoms of a network built from PCH_2CH_2P structural units. Such interconversions of terminal groups in poly(tertiary phosphines) are demonstrated in this paper by syntheses of several poly(tertiary phosphines) containing terminal methoxy groups by methanolyses of the corresponding poly(tertiary phosphines) containing terminal dimethylamino groups.

Experimental Section

Microanalyses were performed by Atlantic Microanalytical Laboratory, Atlanta, Ga., and Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. Proton NMR spectra (Table I) were taken in $CDCl_3$ solution and were recorded either at 100 MHz on a Varian HA-100 spectrometer or at 60 MHz on a Perkin-Elmer Hitachi R-20 spectrometer. Phosphorus-31 (Table II) and carbon-13 (Table III) NMR spectra were taken in dichloromethane solutions unless otherwise indicated and recorded at 40.3 and 25.0336 MHz, respectively, on a Jeolco PFT-100 spectrometer operating in the pulsed Fourier transform mode with proton noise decoupling and a deuterium lock. Spectroscopic measurements on solutions of methyl poly(tertiary phosphines), $(C_2H_5)_2NP(CH=CH_2)_2$, $[(CH_3)_2N]_2PCH=CH_2$, and $C_6H_5P(H)CH_2CH_2P[N(CH_3)_2]_2$ in chlorinated solvents, particularly $CDCl_3$, must be done on freshly prepared solutions, since chlorinated solvents react slowly with these phosphines upon standing at room temperature.

All reactions were carried out in an efficient hood. For reactions using phosphine, methylphosphine, or dimethylphosphine two aqueous calcium hypochlorite traps in series were used to decompose the effluent vapors before passing them into the hood exhaust. A nitrogen atmosphere was always provided for the following three operations: (a) carrying out reactions; (b) handling air-sensitive organophosphorus compounds; and (c) filling evacuated vessels containing potentially air-sensitive materials. When necessary a glove box was used to provide an inert atmosphere. High vacuum distillations were performed