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Rates and Mechanisms of Hydrolysis of Esters of Phosphorous Acid

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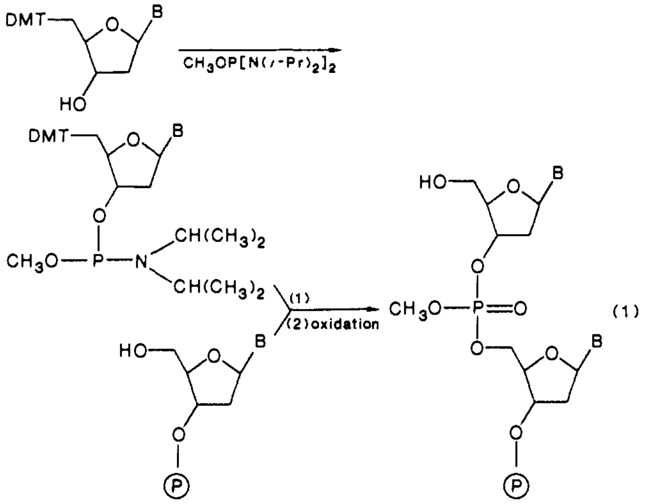
Abstract: Trialkyl phosphites hydrolyze in alkali several hundred times as fast as do the corresponding phosphates; in acid, however, the phosphite hydrolyzes 10^{12} times as fast as the phosphate. Dialkyl phosphites (i.e., dialkyl hydrogen phosphonates) hydrolyze in alkali more than 10^5 times as fast as do the corresponding triesters, presumably by way of metaphosphites as intermediates. The mechanisms of these various processes are discussed. The data are of interest in connection with the phosphite syntheses of DNA.

The rapid advance of molecular biology owes much to the synthesis of DNA invented by Letsinger and co-workers[1] and improved and developed by Caruthers and co-workers.[2] This synthesis operates by way of phosphites or by way of phosphoramidites, where the addition of each nucleoside residue is followed by oxidation of the phosphite to phosphate; the resulting phosphates are quite stable under the operating conditions of the syntheses. The Caruthers synthesis, which uses phosphoramidites, is outlined in eq 1.



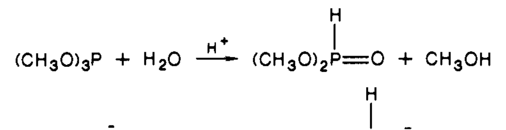
(1)

Many rate data and some speculation concerning the physical–organic chemistry of phosphites are scattered throughout the literature. In this paper some of these data are assembled, some data previously available only in the otherwise unpublished thesis of one of us (F.C.) and some modern NMR spectra are added, and the mechanisms of the processes are discussed. Although these data are not directly applicable to the synthesis shown in eq 1, they are relevant to it.

Results

The rate constants for the alkaline hydrolysis of some phosphites, phosphates, hydrogen phosphonates, and alkylphosphonates are presented in Tables I and II. In analyzing these data, one needs to know the products obtained and, with respect to each of the hydrolyses, whether it proceeds with P–O or C–O cleavage, since comparisons of rate constants are of little mechanistic significance unless the processes that are under comparison are similar.

The hydrolyses of trialkyl phosphates in both acid and base proceed to dialkyl phosphates.[3] The hydrolyses of trialkyl phosphites in acid likewise proceed to dialkyl phosphites but the hydrolysis of trialkyl phosphites in alkali leads to the formation of the anions of the monoalkyl esters of hydrogen phosphonate.[4]



$$(CH_3O)_3P + H_2O \xrightarrow{H^+} (CH_3O)_2\overset{H}{\overset{|}{P}}{=}O + CH_3OH$$

$$(CH_3O)_3P + {}^-OH + H_2O \longrightarrow CH_3O—\overset{H}{\overset{|}{P}}O_2{}^- + 2CH_3OH \tag{2}$$

The data in the Table I show that dimethyl hydrogen phosphonate undergoes alkaline hydrolysis 2 × 10^4 times as fast as does trimethyl phosphite and 2 × 10^5 times as fast as does dimethyl methylphosphonate; these unexpected results, although they must be explained, account for the alkaline hydrolysis of trimethyl phosphite to the anion of monomethyl hydrogen phosphonate rather than to the dimethyl ester. The processes are demonstrated by the proton-coupled ^{31}P NMR spectra shown in Figure 1. In Figure 1A, the spectrum is presented for a reaction mixture made with a few percent excess of 1.0 M alkali and quenched with bicarbonate after 6 min at room temperature (calculated for essentially complete reaction—no phosphite odor). The major spectrum, quartets at −129.75 and −135.05 ppm relative to that of trimethyl phosphate, is that of methyl hydrogen phosphonate; the quartets arise from P–H coupling ($^3J_{H-P}$ = 12 Hz) from the protons of the methyl group, and the large splitting between the quartets arises from the P–H coupling ($^1J_{H-P}$ = 666 Hz) with the hydrogen attached to phosphorus. The very small doublet (−135.25 and −140.05 ppm relative to trimethyl phosphate, with $^1J_{H-P}$ = 582 Hz) has been enlarged 8-fold in the integration; it arises from less than 1% of the dianion of phosphorus acid, or more properly the dianion of hydrogen phosphonate, $HPO_3{}^{2-}$. Even in the carbonate–bicarbonate buffer at pH 11.5, this peak grows slowly and after 24 h at room temperature constitutes about 20% of the total. Figure 1B shows a similar spectrum, but one where the amount of alkali was less than 1 equiv. In the acid environment that results toward the end of the reaction, after the alkali is spent, dimethyl hydrogen phosphonate is stable, and its ^{31}P NMR spectrum appears as two septets, at −124.67 and −130.41 ppm relative to that of trimethyl phosphate ($^3J_{H-P}$ = 12 Hz, $^1J_{H-P}$ = 697 Hz). The enlarged portion of the spectrum clearly shows the septets that arise from coupling of phosphorus with the six hydrogen atoms of the two methyl groups of the diester.

The hydrolysis of trimethyl phosphite is subject to general-acid catalysis;[4] a graph of some of the data is presented in Figure 2. The hydrolysis of dimethyl hydrogen phosphonate is subject both

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(1) Letsinger, R. L.; Mahadevan, V. *J. Am. Chem. Soc.* **1965**, *87*, 3526. Letsinger, R. L.; Ogilvie, K. K. *J. Am. Chem. Soc.* **1967**, *89*, 4801. Letsinger, R. L.; Caruthers, M. H.; Miller, P. S.; Ogilvie, K. K. *J. Am. Chem. Soc.* **1967**, *89*, 7146. Letsinger, R. L.; Ogilvie, K. K. *J. Am. Chem. Soc.* **1969**, *91*, 3350. Letsinger, R. L.; Lunsford, W. B. *J. Am. Chem. Soc.* **1976**, *98*, 3655.

(2) Matteucci, M. D.; Caruthers, M. H. *Tetrahedron Lett.* **1980**, *21*, 719. Matteucci, M. D.; Caruthers, M. H. *J. Am. Chem. Soc.* **1981**, *103*, 3185. Barone, A. D.; Tang, J.-Y.; Caruthers, M. H. *Nucleic Acids Res.* **1984**, *12*, 4051. Caruthers, M. H.; McBride, L. J.; Bracco, L. P.; Dubendorff, J. W. *Nucleosides Nucleotides* **1985**, *4*, 95. Caruthers, M. H. *Science (Washington, D.C.)* **1985**, *230*, 281.

(3) Cox, J. R., Jr.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 317.

(4) Covitz, F. Thesis, Harvard, 1965.

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Table I. Rates of Alkaline Hydrolysis

compd	*T*, °C	*k*, M s^{-1}	*E*, kcal/mol	ratio[i]
trimethyl phosphate[a]	35	3.36×10^{-4}	16.2	
trimethyl phosphate	2[g]	1.44×10^{-5}		
trimethyl phosphite[b]	2	$(8.4 \pm 0.5) \times 10^{-3}$		5.8×10^{2}
triethyl phosphate[a]	37.5	3.73×10^{-5}	15.0	
triethyl phosphate	50[g]	9.47×10^{-5}		
triethyl phosphite[c]	50	3.7×10^{-2}		3.9×10^{2}
dimethyl methylphosphonate[d]	50	1.46×10^{-2}	13.5	
dimethyl methylphosphonate	20[g]	1.72×10^{-3}		
dimethyl hydrogen phosphate[e]	20	3.5×10^{2}		2.0×10^{5}
diethyl methylphosphonate[d]	50	2.6×10^{-3}	11.6	
diethyl methylphosphonate	25[g]	4.2×10^{-4}		
diethyl hydrogen phosphate[f]	25	3.5×10^{2}		3.1×10^{5}
diethytl hydrogen phosphonate (H exchange)[l]	20	2.5×10^{5}		
diethyl hydrogen phosphonate (H exchange)	25[h]	3.2×10^{5}		2.5×10^{3} (relative to hydrolysis)

[a] Cox, J. R., Jr.; Ramsay, O. B. *Chem. Rev.* **1964**, *64*, 317. [b] Covitz, F. Ph.D. Thesis, Harvard University, 1965. These measurements were made in 40% isopropyl alcohol–60% water by volume. [c] Bel'skii, V. E.; Motygullin, G. Z. *Bull. Acad. Sci. U.S.S.R.* (*Engl. Transl.*) **1967**, 2427. [d] Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1956**, 2521. [e] Nylen, P. *Svensk. Kem. Tid.* **1937**, *49*, 29, 79. [f] Hammond, P. R. *J. Chem. Soc.* **1962**, 1365. [g] Extrapolated. [h] Estimated. [i] Rate constant for the hydrolysis of a phosphite divided by that of the corresponding phosphate or phosphonate, extrapolated to the same temperature, except where otherwise indicated.

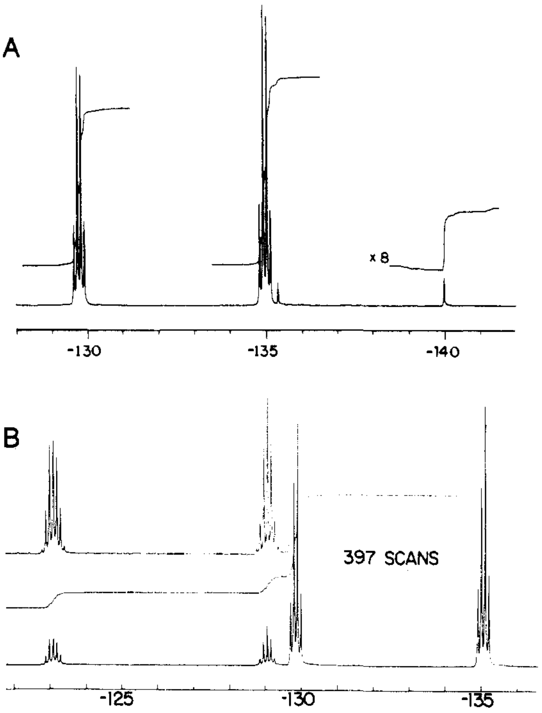

Figure 1. (A) ^{31}P NMR spectrum of the products of the hydrolysis of trimethyl phosphite in the presence of a few percent excess alkali. The quartets at −129.75 and −135.05 ppm relative to trimethyl phosphate arise from the monoanion of monomethyl hydrogen phosphonate, with $^{3}J_{H-P} = 12$ Hz and $^{1}J_{H-P} = 666$ Hz. The small peaks at −135.25 and −140.05 ppm relative to trimethyl phosphate, $^{1}J_{H-P} = 582$ Hz, arise from less than 1% of the dianion of phosphorous acid. (B) ^{31}P NMR spectrum of the products of the hydrolysis of trimethyl phosphite in the presence of slightly less than 1 molar equiv of alkali. A trace of acid was added before the spectrum was taken. The two quartets arise from the monoanion of methyl hydrogen phosphonate, as in (A). The multiplets at −124.67 and −130.41 ppm, with $^{1}J_{H-P} = 12$ Hz and $^{3}J_{H-P} = 697$ Hz, arise from dimethyl hydrogen phosphate; the enlarged portion of the spectrum clearly shows that these multiplets are septets.

Table II. Rates of Acid Hydrolysis

compd	*T*, °C	*k*, M s^{-1}	ratio[d]
triethyl phosphate[a]	79.7	2.1×10^{-6}	
triethyl phosphate	2[c]	3.2×10^{-10}	
trimethyl phosphate[b] (H^+)	2	3.0×10^{2}	1.0×10^{12}
trimethyl phosphite[b] (HOAc)	2	0.058	

[a] Lyznicki, E. P., Jr.; Oyama, K.; Tidwell, T. T. *Can. J. Chem.* **1974**, *52*, 1066. Bel'skii, V. E.; Pudovik, A. N.; Efremova, M. V.; Elisenkov, V. N.; Panteleva, A. R.; *Dokl. Akad. Nauk. S.S.S.R.* **1968**, *180*, 351. The rate constants of Lyznicki et al. were obtained in 35% dioxane–65% water. [b] Covitz, F. Ph.D. Thesis, Harvard University, 1967. These measurements were made in 40% isopropyl alcohol–60% water. [c] Estimated. [d] Rate constant for the hydrolysis of trimethyl phosphite divided by that for trimethyl phosphate, extrapolated to the same temperature.

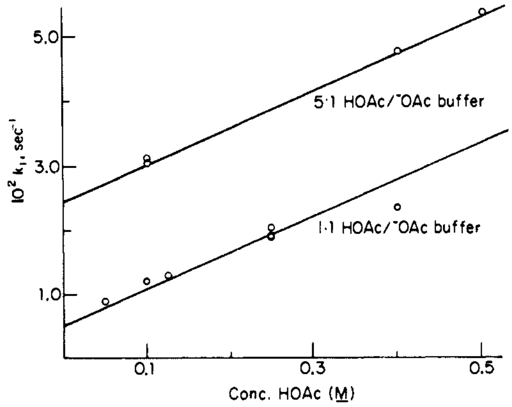

Figure 2. General-acid catalysis in the hydrolysis of trimethyl phosphite in 40% isopropyl alcohol–60% water by volume at 2 °C in acetic acid–sodium acetate buffers. An ionic strength of 0.50 was maintained in all buffers with sodium perchlorate.

to general-acid catalysis and to general-base catalysis,[5] and these data are discussed below.

All of the data in Tables I and II, except those for the acid-catalyzed hydrolysis of trimethyl and triethyl phosphate, refer to cleavage exclusively at the P–O bond. This fact was established with respect to the cleavages of trialkyl and dialkyl phosphites in both alkali and acid by Gerrard and co-workers,[6] who prepared phosphite, phosphate, and phosphonate esters of optically active *sec*-octyl alcohol and showed that the hydrolyses proceed with complete retention of configuration of the alcohol. Although corresponding experiments have not been carried out with methyl and ethyl esters, one can reasonably extrapolate from the vast body of physical–organic chemistry to conclude that if C–O cleavage in acid does not occur with a secondary alkyl group, it will not occur with a primary one. The hydrolyses of the trialkyl esters of phosphoric acid are not so clean; experiments[7] with water

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(5) Nylen, P. *Svensk. Kem. Tid.* **1937**, *49*, 29, 79. Hammond, P. R. *J. Chem. Soc.* **1962**, 2521. Bel'skii, V. E.; Motygullin, G. Z. *Bull. Acad. Sci. U.S.S.R.* (*Engl. Transl.*) **1967**, 2427.

(6) Gerrard, W.; Green, W. J.; Nutkins, R. A. *J. Chem. Soc.* **1952**, 4076.

(7) Blumenthal, E.; Herbert, J. R. M. *Trans. Faraday Soc.* **1945**, *41*, 61. Efrimov, Y. Y.; Efrimova, M. V.; Bel'skii, V. E. *Bull. Acad. Sci. U.S.S.R.* (*Engl. Transl.*) **1969**, 666.

labeled with ^{18}O have shown that, although the alkaline hydrolysis of trimethyl phosphate proceeds exclusively with P–O cleavage, triethyl phosphate is cleaved under acid catalysis with at least 70% C–O cleavage; further, hydrolysis of tri-*sec*-octyl phosphate in acid proceeds largely, although not completely, with racemization of the alcohol.[6] The slight excess of retention over inversion that Gerrard and co-workers reported for the hydrolysis of tri-*sec*-octyl phosphate suggests some P–O cleavage, in accord with the results with ^{18}O reported by Blumenthal and Herbert.[7]

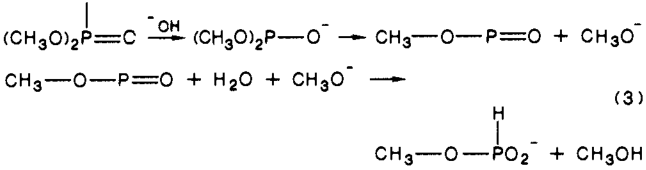
The hydrolysis of triethyl phosphate responds to acid catalysis only under very strongly acidic conditions, with perchloric acid[8] and a mixed aqueous–organic solvent; moderately concentrated aqueous sulfuric acid does not cause any acceleration. What one then knows about the acid-catalyzed hydrolysis of triethyl phosphate is that the rate of cleavage at the P–O bond is less, and possibly substantially less, than the total measured rate, most of which refers to C–O cleavage. The ratio of the rate constant for hydrolysis with P–O cleavge of trimethyl phosphite relative to that for the P–O cleavage of triethyl phosphate is therefore greater, and possibly substantially greater, than the quotient of the measured rate constants presented in Table I; notably, this minimum quotient is 10^{12}.

The acid-catalyzed hydrolysis of triethyl phosphate was carried out in 35% dioxane–65% water, and the hydrolysis of trimethyl phosphite in both acid and base was carried out in 40% isopropyl alcohol–60% water. For want of completely comparable data, the rate of acid-catalyzed hydrolysis of trimethyl phosphite has been compared with that of triethyl phosphate. However, the data in the review by Cox and Ramsay[3] show that neither the change of ester nor the change of solvent within these narrow limits has a large effect on reaction rates. Since the rate constants listed in Table II differ by such a large factor, they were necessarily measured at different temperatures, so that the calculation requires a long extrapolation from higher temperature where the rate for hydrolysis of the phosphate was observed to lower temperature where the rate for the phosphite was measured; similar, if less extended, extrapolation is required for many of the comparisons in Table I. Nevertheless, the uncertainties introduced by all the problems above are so small in comparison to the enormous rate factors under discussion that they can reasonably be neglected.

Discussion

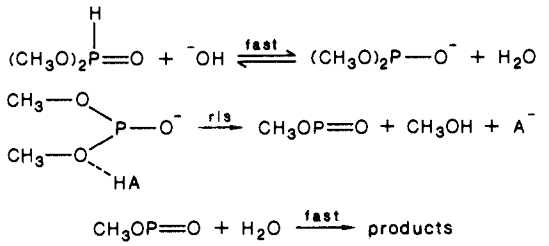
We wish to explain the following: (1) the greater rate constants for the hydrolysis in alkali of phosphites relative of those of phosphates and methylphosphonates, (2) the enormous factor of 10^{12} by which the rate constant for the hydrolysis of a trialkyl phosphite exceeds that of a trialkyl phosphate under acid catalysis, (3) the large factor (greater than 10^5) by which the rate of hydrolysis of dialkyl hydrogen phosphonates exceeds those of trialkyl phosphites, and (4) the finding of general-acid and general-base catalysis for the hydrolysis of hydrogen phosphonates. This discussion will start with (3) and (4).

The rate of alkaline hydrolysis of dimethyl hydrogen phosphonate exceeds that for dimethyl methylphosphonate by a factor of 2×10^5 and exceeds that of trimethyl phosphate by a factor of about 10^4; these large rate factors almost certainly arise because the hydrogen atom attached to phosphorus in the hydrogen phosphonate can ionize, whereas no such ionization is possible with either the triester of phosphorus acid or with the diesters of methylphosphonate.[9] The possibility that the difference is caused by steric hindrance appears remote. First and foremost, the general-base catalysis that Nylen[5] observed is best explained (see below) by the ionization of the hydrogen phosphonate. Second, although steric hindrance has been observed[10] in the hydrolysis of phosphonates, it is only important with very large groups. The acidity of the hydrogen atom attached to phosphorus is relevant to this discussion. Although the p*K* of diethyl hydrogen phosphonate has never been measured directly, it has been estimated[11,12] as around 14.6, so that the compound should be slightly, but only slightly, ionized in dilute alkali. (The rate of alkaline hydrolysis of a dialkyl hydrogen phosphonate is not compared with that for the corresponding dialkyl phosphate anion because the latter is negatively charged; this charge reduces the rate of hydrolysis relative to that of trimethyl phosphate by an additional factor of 10^5, but that additional factor is easily understood as an electrostatic effect.[13]) Presumably the dimethyl phosphite anion, produced from the hydrogen phosphonate in alkali, is highly reactive. In 1963, Kaiser, Panar, and one of us[14] suggested that the anion of dimethyl hydrogen phosphonate fragments, to produce metaphosphite as an intermediate in the hydrolysis.



$$(CH_3O)_2P(H){=}C \xrightarrow{^-OH} (CH_3O)_2P{-}O^- \rightarrow CH_3{-}O{-}P{=}O + CH_3O^-$$
$$CH_3{-}O{-}P{=}O + H_2O + CH_3O^- \rightarrow CH_3{-}O{-}P(H)O_2^- + CH_3OH \quad (3)$$

This explanation must, however, be refined. If the anion spontaneously fragmented, as shown in eq 3, then the rate of alkaline hydrolysis of dimethyl hydrogen phosphonate would be strictly proportional to the concentration of alkali at any value of pH that is substantially less than the p*K* of the hydrogen phosphonate.[11,12] Nylen found, however, that the hydrolysis of dimethyl hydrogen phosphonate is general-acid and general-base catalyzed.[5] This might at first suggest that the rate-limiting step is the abstraction of the proton from the hydrogen phosphonate. Such an explanation, however, cannot be valid, since the rate of hydrogen–deuterium exchange[15] for dimethyl hydrogen phosphonate is about 2500 times as great as the rate of hydrolysis. Further, the rate of oxidation by iodine, which is alkali catalyzed, is also much faster than hydrolysis.[12,16] A reasonable mechanism is shown in eq 4.



$$(CH_3O)_2P(H){=}O + {^-OH} \xrightleftharpoons{\text{fast}} (CH_3O)_2P{-}O^- + H_2O$$
$$(CH_3{-}O)(CH_3{-}O\cdots HA)P{-}O^- \xrightarrow{\text{rls}} CH_3OP{=}O + CH_3OH + A^- \quad (4)$$
$$CH_3OP{=}O + H_2O \xrightarrow{\text{fast}} \text{products}$$

This mechanism posits general-acid catalysis of the decomposition of the anion, a sequence that is of course kinetically equivalent to general-base catalysis of the neutral substrate. This suggestion implies that the loss of methanol from dimethyl phosphite anion is rapid relative to the loss of methoxide ion and similarly applies to the ethyl esters with which Nylen worked; it fits all of the kinetic data.

The most spectacular of the rate data concern the acid catalysis of the hydrolysis of trimethyl phosphite. This compound is extraordinarily sensitive to acid-catalyzed hydrolysis. The rate constant for hydrogen ion catalysis[4] is around 300 M^{-1} s^{-1} at 2 °C and was obtained from the rates in acetic acid–sodium acetate. The reaction is subject to general-acid catalysis, so extrapolation of the data for each buffer ratio to zero buffer concentration yields the rate at a particular hydrogen ion concentration; since these data were obtained with acetic acid–sodium acetate buffers, all the hydrogen ion concentrations are in the neighborhood of 10^{-5}

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(8) Lyznicki, E. P., Jr.; Oyama, K.; Tidwell, T. T. *Can. J. Chem.* **1974**, *52*, 1066.

(9) Hammond, P. R. *J. Chem. Soc.* **1962**, 2521.

(10) Hudson, R. F.; Keay, L. *J. Chem. Soc.* **1956**, *2463*.

(11) Guthrie, J. P. *Can. J. Chem.* **1979**, *57*, 236.

(12) Lewis, E. S.; Spears, L. G., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 3918.

(13) Westheimer, F. H. *Science (Washington, D.C.)* **1987**, *237*, 1173. Kirkwood, J. G.; Westheimer, F. H. *J. Chem. Phys.* **1938**, *6*, 506. Westheimer, F. H.; Kirkwood, J. G. *J. Chem. Phys.* **1938**, *6*, 513.

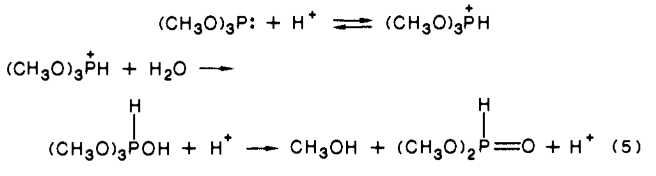
(14) Kaiser, E. T.; Panar, M.; Westheimer, F. H. *J. Am. Chem. Soc.* **1963**, *85*, 602.

(15) Hammond, P. R. *J. Chem. Soc.* **1962**, 1365.

(16) Nylen, P. *Z. Anorg. Allg. Chem.* **1938**, *235*, 161.

M. The quotients of these extrapolated rate constants by the appropriate hydrogen ion concentrations yield the rate constant for second-order hydrogen ion promoted hydrolysis.

Why should the rate constant for acid-catalyzed hydrolysis be so enormous? First and foremost, the phosphorus atom in trimethyl phosphite holds an unshared electron pair and will presumably react with protons to form a phosphonium salt. Although the basicity of trimethyl phosphite has not been measured, the large number of, and equilibrium constants for, the metal-ion complexes that it forms[17] are ample proof of its nucleophilic character. Guthrie[18] suggests that the pK probably lies around zero, with a crudely estimated uncertainty of around 2 log units; this value of the pK is based primarily on an estimate of -4.6 for the pK_a of O-protonated diethyl hydrogen phosphonate and on his prior estimate of the constant of 1.6×10^7 for the conversion of $(CH_3O)_2POH$ to $(CH_3O)_2PHO$, together with a number of estimated corrections. The phosphonium salt (i.e., the protonated phosphite) will rapidly add water to form a phosphorane, and this will then cleave to product. The actual rate constant that must be postulated here is probably more or less consistent with that observed for the hydrolysis of methyltriphenoxyphosphonium triflate. The rate constant for reaction of that salt with water at 25 °C has been obtained[19] by extrapolation from rates measured in acetonitrile–water mixtures to about 10^4 s^{-1}; the rate of hydrolysis of triethyl phosphite in 1 M acid at 2 °C is calculated[4] as about 300 s^{-1}. Since the fraction of the phosphite that will be protonated is unknown, and since the relative rate of attack of water on methoxy as contrasted to the phenoxyphosphonium salts is unkown, and since the temperature factor can only be estimated, the rate of decomposition of the cationic intermediate cation in the acid-catalyzed hydrolysis of the phosphite is uncertain but is in any event large and reasonable in the light of the rate for phosphonium salts.



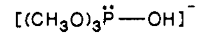
$$(CH_3O)_3P\!: + H^+ \rightleftharpoons (CH_3O)_3\overset{+}{P}H$$
$$(CH_3O)_3\overset{+}{P}H + H_2O \longrightarrow$$
$$(CH_3O)_3\overset{H}{\overset{|}{P}}OH + H^+ \longrightarrow CH_3OH + (CH_3O)_2\overset{H}{\overset{|}{P}}{=}O + H^+ \quad (5)$$

The catalysis by acetic acid of the hydrolysis of trimethyl phosphite probably proceeds by way of attack of acetate ion on the protonated phosphite, with subsequent rapid hydrolysis of the resulting mixed phosphorus–acetic acid anhydride. Here attack by a Brønsted base on a protonated intermediate is kinetically equivalent to general-acid catalysis. An alternative but less likely mechanism for the acid-catalyzed hydrolysis of trimethyl phosphite would allow the reaction to proceed, via protonation on oxygen, by way of a metaphosphite cation. Such a mechanism is hard to reconcile with general-acid catalysis and, in any event, would be more probable for the reactions of the phosphoramidites, with protonation on nitrogen rather than on oxygen.

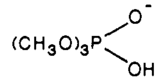
By contrast to the acid-catalyzed hydrolysis of phosphites, where the compound can be protonated on phosphorus, the acid-catalyzed hydrolysis of phosphates and methylphosphonates must be preceded by protonation on oxygen. Because of the greater stability of the phosphoryl group, this protonation is quite unfavorable, so that the concentration of the phosphonium compound will be quite low. Even when protonation has been achieved, the resulting positive charge is not as highly concentrated on phosphorus, so that the attack of a nucleophile such as water on the phosphorus atom will not occur so readily as on that of a protonated phosphite. Experimentally, the acid-catalyzed attack of water on phosphates hardly occurs at all; as noted above, phosphate esters are highly resistant to acid-catalyzed hydrolysis, and when the reaction does occur, it occurs largely, although probably not entirely, with C–O cleavage.

As shown in eq 1, the Caruthers modification of the Letsinger synthesis utilizes phosphoramidites in place of phosphites. The physical–organic chemistry here has not yet been elucidated, but one would anticipate similar behavior for the phosphoramidites as for the phosphite esters, except that the phosphoramidites will be more basic, and therefore even more sensitive to acid, than phosphites. Subsequent to oxidation of phosphite to phosphate, or of phosphoramidite to phosphoramidate, the resulting compounds are extraordinarily resistant to acid-catalyzed reactions.

Finally, we must explain why the rates of alkaline hydrolysis of triesters of phosphorus acid exceed those of the corresponding esters of phosphoric acid by a factor of about 300. Attack of hydroxide on a phosphate produces an intermediate phosphorane[20] with negative charge on oxygen; attack on a phosphite may occur by a direct displacement or by way of a phosphorane with negative charge directly on phosphorus. One might have anticipated that negative charge would be more stable on oxygen than on phosphorus; that is to say, ion B would be expected to be more stable than A. But even if this assumption is correct, presumably the phosphate is a much more stable starting material than the phosphite and resists attack of hydroxide ion. The free energy of activation is the difference between the free energy of the transition state and that of the starting material; an extremely stable starting material reacts slowly.



A



B

Experimental Section

Materials. Trimethyl phosphite was obtained from Aldrich and vacuum fractioned before use. Dimethyl hydrogen phosphonate was synthesized according to McCombie et al.;[21] it boiled at 73–74/14 mm. Other chemicals were reagent grade.

NMR Spectra. The proton-coupled ^{31}P NMR spectra were obtained with a Bruker WM 300 spectrometer, operated at 121 MHz (300 MHz for hydrogen) and at room temperature (about 20 °C).

pH. For those reactions carried out in 40% isopropyl alcohol, the "pHs" of buffer solutions were measured separately in that solvent. The measurements were made on a Radiometer pH meter calibrated at "pH" 3.00 with 0.00100 M perchloric acid and 0.500 M sodium perchlorate in the same mixed solvent. The 5:1 buffer of acetic acid–sodium acetate had an average "pH" (determined as described above) of 4.15 and the 1:1 buffer an average "pH" of 4.89. The ionization constant of acetic acid in 40% aqueous isopropyl alcohol is then approximately 1.36×10^{-5} M.

Reaction Rates. The rates of reaction were determined calorimetrically, with the same stirring calorimeter and with the same methodology as that for previous work from this laboratory.[14,22] The sample for a kinetic experiment was enclosed in a fragile glass ampule that was inserted into the stirrer assembly together with the alkali or buffer with which the phosphite would react, and the calorimetric assembly was closed and sealed. The sample of phosphite and the alkali or buffer were then allowed to come to temperature equilibrium with the thermostat (several hours). Temperature was measured, as previously, with a thin, glass-encased thermistor (Fenwal GA51P8), and its resistance was measured with a conventional Wheatstone bridge. The reaction was started by pushing the ampule, in the stirrer assembly, against a sharp point within the calorimeter that was designed to smash the ampule. A very rapid initial change in temperature was caused by breaking the ampule and by the solution of the phosphite in the solvent; this was followed by a regular increase in temperature as the reaction proceeded. Since the temperture rise was restricted to 0.5 °C or less, and since the rate constant increases only about 1% with an increase of temperature of 1 °C, the assumption was made that the extent of reaction was proportional to the rise in temperature, and no corrections[22] were made in

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the calculations for temperature rise. Corrections were made graphically for heat leak where appropriate; since the heat leak for the calorimeter was about 5×10^{-5} s^{-1} (half-time for cooling of about 200 min) reactions with half-lives of as much as 20 min could conveniently be followed. Since the response lag of all the various components of the calorimeter was only a few seconds, rates could be measured for reactions with half-lives of only a fraction of a minute.

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Registry No. Trimethyl phosphate, 512-56-1; trimethyl phosphite, 121-45-9; triethyl phosphate, 78-40-0; triethyl phosphite, 122-52-1; dimethyl methylphosphonate, 756-79-6; dimethyl hydrogenphosphonate, 868-85-9; diethyl methylphosphonate, 683-08-9; diethyl hydrogenphosphonate, 762-04-9.

Thin-Layer Phase-Transfer Catalysis in the Reaction of Alkyl Chlorides and Solid Formate Salt

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Abstract: A systematic study of the quaternary ammonium catalyzed solid–liquid esterification of alkyl chlorides by alkali formate has been undertaken. The maximum conversion and the kinetics of the reaction were found to be strongly dependent on the type of formate salt used. The reaction rate was highest when a definite amount of water was added. The optimal water content varied strongly when the inorganic cation, the reaction temperature, or the catalyst concentration was changed. When the amount of water was limited, most of it was found surprisingly in the organic phase as water of hydration of the quaternary ammonium ion pair, reducing the rate of the homogeneous reaction step. At very low water concentrations the overall rate was limited by slow mass transfer, which could be enhanced by application of ultrasound.

The coextraction of water in liquid–liquid phase-transfer catalysis (PTC) has a negative influence on certain types of reactions.(1-3) Two methods have been suggested to solve this problem. One of them, the application of highly concentrated aqueous solutions of KOH and NaOH,(4,5) suffers from catalyst decomposition when onium salts are used as catalysts. Therefore the second, the use of solid–liquid systems, is widely employed.(1,6-8) It is quite surprising that only very little effort has been made to evaluate the influence of various parameters on this type of reaction. It has been found by different workers that the reaction velocity in various systems is a function of the amount of water employed and that an optimum amount of water results in the fastest rates.(8-12) Since the influence of various reaction parameters on this optimum amount has not been tested, the conclusions drawn were quite limited. Furthermore, the amount of water present is generally represented as a fraction of the solid phase,(8-11) thereby suggesting that this is its actual location in the system, although this has never been examined.

It has been proposed that in the presence of a slight amount of water, dissolution of the inorganic salt in the aqueous film precedes the ion exchange with the catalyst salt.(9,13) If this is true, then the kinetics of the overall reaction should be strongly dependent on the relative solubilities of the attacking (Y^-) and the displaced (X^-) ions in this film, as can be seen from eq 1 and 2,(14) where Q represents the quaternary onium cation.

$$-d[RX]/dt = k_2[RX][QY] \tag{1}$$

$$[QY] = [QX]_{org}K^{sel}_{Y/X}\frac{[Y^-]_{aq}}{[X^-]_{aq}} \tag{2}$$

Table I. Solubility Ratio and Formation of Decyl Formate with Different Formate Salts[a]

type of cation[b]	solubility ratio[c]	max conversion (%) after 48 h	rate constant (min^{-1}) $\times 10^3$
Ca^{2+}	0.1	0%	
Li^+	0.4	11%	0.1[d]
Na^+	4	98%	2.0[e]
K^+	12	100%	11.4[e]

[a] Reaction conditions: chlorodecane, 18 mmol; Aliquat, 1.05 mmol, made up to 12.0 mL with *o*-dichlorobenzene; inorganic formate (36 mmol)–1% (w/w) H_2O; mechanical agitation at 800 rpm; 100 °C. [b] The data obtained with ammonium formate are irrelevant due to (a) sublimation of the solid out of reach of the organic phase and (b) formation of formic acid by hydrolysis of the salt, which causes depression of the substitution reaction.(17) [c] Ratio of solubilities of formate and chloride salts, at 100 °C.(16) [d] Approximate pseudo-first-order rate constant. [e] Pseudo-first-order rate constant.

This correlation between solubility and reaction rate has been confirmed experimentally.(15)

Recently, it has been shown that the maximum conversion obtainable in different solid–liquid exchange reactions varies with the amount of water present in the system.(9,11,13) In the case of bromide/chloride exchange the results could be correlated to the

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