# The Hydrolysis of Dinitrophenyl Phosphates[1a,b]

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**Abstract:** The hydrolyses of the 2,4- and 2,6-dinitrophenyl phosphates differ from those of other aryl phosphates in that the dianion is more reactive than the monoanion. For 2,5-dinitrophenyl phosphate these two species have similar reactivities, but the hydrolysis of the dianion becomes more important at higher temperatures. Both reactions appear to involve elimination of a hypothetical metaphosphate intermediate, although the products of solvolyses of the dianions in aqueous methanol or ethanol show that it reacts preferentially with the alcohol. Attack of hydroxide or alkoxide ion upon the dianions also occurs, and in alkaline methanol there is nucleophilic attack upon the aryl group. There are rate maxima at 6–7 *M* acid, depending upon the acid and substrate.

As part of a general study of the hydrolyses of phosphate esters,[3,4] we have prepared 2,4-, 2,5-, and 2,6-dinitrophenyl phosphates in order to study their mechanisms of chemical and enzymic hydrolyses. This paper deals with the chemical hydrolyses. The hydrolyses of most simple aryl and alkyl phosphates show a rate maximum at pH 4, where the phosphates are present wholly as monoanions $ROPO_3H^-$, whose reactivities are relatively insensitive to the nature of the group R.[5] These phosphates are usually unreactive at high pH unless a neighboring group is present,[4,5] or unless elimination is the predominant reaction.[6] There is an increase of hydrolysis rate of *p*-nitrophenyl phosphate with increasing pH in alkaline solution, owing either to attack of hydroxide ion or decomposition of a phosphate dianion.[3,7] Phosphoric–carboxylic anhydrides can react by a mechanism which most probably involves decomposition of the dianion.[8]

The monoalkyl and monoaryl phosphates behave quite differently at low pH. Hydrolyses of the former are catalyzed by strong acids,[4,5,9] but hydrolyses of the monoaryl phosphates are acid catalyzed only when there is an electron-withdrawing substituent ($NO_2$ or $COCH_3$) in the phenyl group, and then there is a rate maximum at acid concentrations of 5–7 *M*, depending upon the catalyzing acid.[3,10–12]

2,4-Dinitrophenol uncouples oxidative phosphorylation in mitochondria,[13] and a number of workers have argued for and against the intermediacy of 2,4-dinitrophenyl phosphate in these reactions.[14,15] Boyer has reported its synthesis and an approximate rate of chemical hydrolysis, and has given reasons for believing that it could not be an intermediate in these biological systems.[15] However, Azerad, Gautheron, and Vilkas have raised questions about this reported preparation, and concluded that 2,4-dinitrophenyl phosphate is a very labile compound.[16]

We have prepared 2,4-, 2,5-, and 2,6-dinitrophenyl phosphates as the cyclohexylamine salts in order to compare their hydrolyses with those of other phenyl phosphates. Another method of preparing 2,4-dinitrophenyl phosphate has recently been reported in preliminary form. The hydrolysis has been examined in the pH range 2–12 and, as in hydrolyses of acyl phosphates,[8] the pH–rate profile was interpreted in terms of decomposition of the dianion to phenoxide and metaphosphate ion being the slow step of the reaction.[17] No acid or alkaline hydrolysis was observed.

## Experimental Section

**Materials.** The dinitrophenyl phosphates were prepared from the phosphoryl dichlorides by treating them with dried silver oxide in dried acetonitrile.

The phosphoryl dichlorides were prepared by a modification of the usual method.[16] Freshly distilled phosphorus oxychloride (0.2 mole) and dry sodium chloride (0.0004 mole) were degassed with dry nitrogen, and dried dinitrophenol (0.025 mole) was then added. The solution was stirred and heated under reflux in a nitrogen stream for 2–3 days. The excess phosphorus oxychloride was removed *in vacuo*, and the aryl phosphoryl dichlorides formed light yellow crystals on standing in a desiccator.

The phosphoryl dichlorides (0.002 mole) were dissolved in 30 ml of freshly distilled acetonitrile, and shaken with an excess of dried silver oxide under dry nitrogen for 1–2 min. The silver oxide and chloride were recovered by filtration and an excess of dry cyclohexylamine hydrochloride was added to the filtrate. The mixture was shaken for 1–2 min and filtered and the acetonitrile removed *in vacuo*. White crystals separated and were washed several times with benzene (by decantation), the residual benzene was then removed by filtration through sintered glass, and the white crystals were dried under vacuum. This treatment gave the monohydrates

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(1) (a) This work was presented in part at the Symposium on Bio-Organic Reactions, American Chemical Society Western Regional Meeting, Los Angeles, Calif., Nov 1965, and is abstracted in part from the thesis of Eleanor J. Fendler, submitted in partial fulfillment of the requirements of the Doctor of Philosophy degree of the University of California, Santa Barbara. (b) This work was supported by the National Science Foundation under GP 2889. This support is gratefully acknowledged.

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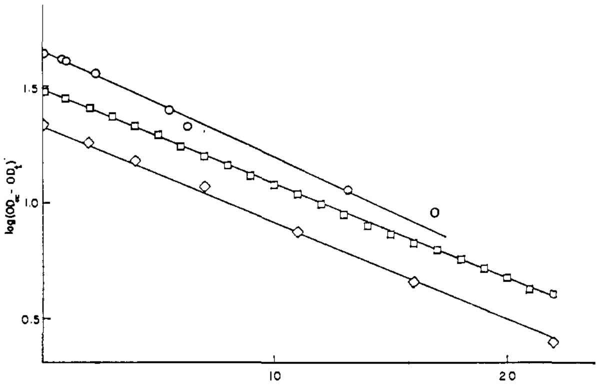

Figure 1. Plot of log ($OD_\infty - OD_t$) against time: □, 2,4-dinitrophenyl phosphate at pH 4.3 at 73.0° (time scale in min); ◇, 2,4-dinitrophenyl phosphate in 2 *M* HCl + 6 *M* LiCl at 73.0° (time scale in min); ○, 2,5-dinitrophenyl phosphate in 1.0 *M* NaOH at 45.0° (time scale in $10^2$ min).

of monocyclohexylamine salts, $(NO_2)_2C_6H_3OPO_3H_2 \cdot C_6H_{11}NH_2 \cdot H_2O$.

*Anal.* Calcd for $C_{12}H_{20}N_3O_9P$: C, 37.8; H, 5.2; N, 11.0; P, 8.1. Found (2,4-): C, 38.3; H, 5.0; N, 10.8; P, 7.8. Found (2,5-): C, 37.7; H, 4.6; N, 11.1; P, 8.0. Found (2,6-): C, 37.4; H, 4.5; N, 10.9; P, 8.1.

They had the following melting points: 2,4-, 147°; 3,5-, 145°; and 2,6-, 146°. Freshly prepared samples were used for the kinetic and product experiments because these aryl phosphates turn slightly yellow on standing, even in a vacuum desiccator.

The 2,4- and 2,6-dinitroanisoles were prepared from the chlorodinitrobenzenes by treatment with sodium methoxide in methanol, and had the following melting points: 2,4-dinitroanisole, 87° (lit.[18] 88°); 2,6-dinitroanisole, 117–118° (lit.[18] 117.5°). 2,4-Dinitrochlorobenzene was a commercial sample, and 2,6-dinitrochlorobenzene, prepared from the phenol and phosphorus oxychloride,[19] had mp 86–87° (lit.[19] 86–88°).

**Solvents.** Solutions for the rate measurements were made up using deionized distilled water. Aqueous–alcohol mixtures were made up by weight to correspond to the quoted volume composition, using the densities at 25°.

**Buffer Solutions.** The pH was measured at 25°, and these values are quoted in the various tables of rate constants.

**Kinetics.** The hydrolysis was generally followed by colorimetric determination of phenoxide ion spectrophotometrically in the thermostated cell compartment of a Cary 14 or a Perkin-Elmer-Hitachi 139 spectrophotometer. For runs at low pH, where the phenol is not fully ionized, samples were added to excess sodium carbonate, and the optical density was then quickly measured. For reactions in strong acid, solutions of Tris or sodium tetraborate were used to increase the pH. The following wavelengths (in A) were used for following phenol formation: 2,4-, 3580;[20] 2,5-, 4400; 2,6-, 4290. The Beer-Lambert law is obeyed at the concentrations used (*ca.* $10^{-4}$ *M*).

For some hydrolyses the cyclohexylamine salt was converted into the free acid by passing it through Dowex 50W-X8 resin in the acid form. Removal of cyclohexylamine did not affect the hydrolysis rate.

In aqueous methanol a few reactions were followed by the evolution of inorganic phosphate, which was determined colorimetrically.[21] Examples of kinetic runs are shown in Figure 1.

**Products.** The product compositions were determined for reactions in alcoholic solutions by the following procedures.

The optical density was measured at 2920 and 3580 A for 2,4-dinitrophenyl phosphate. At these wavelengths the extinction coefficients of 2,4-dinitrophenoxide ion are 1000 and 5800, respectively, and of 2,4-dinitroanisole are 10,900 and 620. For 2,6-dinitrophenyl phosphate the wavelengths were 3450 and 4290 A, where the extinction coefficients of the 2,6-dinitrophenoxide ion are 1800 and 8100, respectively, and of 2,6-dinitroanisole 950 and 100. These extinction coefficients were all measured in 0.1–0.4 *M* sodium methoxide in methanol, and in this range were unaffected by concentration of methoxide ion. From these measurements we can calculate the relative amounts of phenol and anisole. In one experiment the amount of 2,4-dinitrophenol was first determined spectrophotometrically as phenoxide ion at 3580 A, and then aqueous alkali was added to hydrolyze any dinitroanisole to the dinitrophenol, which was then redetermined. In this experiment inorganic phosphate was determined colorimetrically.[21]

The formation of 2,4- and 2,6-dinitroanisoles was confirmed gas chromatographically, using a 1-m glass column, 0.25 in. i.d., packed with 2% Versamid 900 (F & M) on Chromosorb W, with temperature programming at 2.5°/min from 100°. Under the conditions, the anisoles had the following retention times: 2,4-dinitro, 29 min; 2,6-dinitro, 28 min. The dinitrophenols were not eluted from the column within 8 hr at 200°. The 2,4- and 2,6-dinitrophenyl phosphates were treated with 0.3 *M* sodium methoxide in methanol, and after acidification the dinitroanisoles were extracted with ether and the extracts analyzed gas chromatographically. The retention times were identical with those of authentic samples and co-injection with the authentic ether gave only one peak.

The products of alkaline reactions of 2,5-dinitrophenyl phosphate were not examined because the phenol loses a nitro group at high pH.

**Solvolyses in Aqueous Alcohol.** For the reactions of the dianions in aqueous methanol or ethanol we used an aqueous borate buffer at pH 8, to which alcohol was added. The pH in the solvent is increased but the products should not be changed, because the pH change should be small.[22] Addition of alcohols to water should decrease the second dissociation constant of the dinitrophenyl phosphates, but again the effect should be small. Juillard has shown that for many weak acids the change in p*K* is less than two units up to 60 mole % of alcohol,[23] and we can assume that in our aqueous alcohol solvents the aryl phosphates will be present wholly as the dianions, because the effects of alcohol upon the dissociation constants of the buffer acid and the aryl phosphate will be self-compensating.

**Dissociation Constants.** We attempted to determine $pK_2$ for 2,4-dinitrophenyl phosphate at 1° by titration using a Leeds and Northrup pH meter with microelectrodes. In one experiment a a solution of the cyclohexylamine salt was treated with Dowex 50W-X8 resin in the acid form, and then titrated quickly with 0.1 *M* sodium hydroxide, and in a second experiment the phosphoryl dichloride was shaken in water until it dissolved, and the acid was then titrated quickly with 0.1 *M* sodium hydroxide. Both experiments gave $pK_2 \sim 4.5$. No attempt was made to measure the dissociation constants of 2,6-dinitrophenyl phosphate because of its high reactivity.

**Hydrolysis of 2,4-Dinitroanisole.** Our hopes of studying the hydrolysis products of these dinitrophenyl phosphates in alkaline aqueous alcohol were frustrated by the alkaline hydrolysis of 2,4-dinitroanisole in aqueous methanol (Table I; *cf.* ref 24). Methoxide is a poor leaving group, but the rates of aromatic nucleophilic substitutions are relatively insensitive to the nature of the leaving group when the rate-limiting step is nucleophilic addition.[25]

**Table I.** Hydrolysis of 2,4-Dinitroanisole

| $CH_3OH$, vol % | $C_{OH^-}$, *M* | $10^5k_\psi$,[a] sec$^{-1}$ |
|---|---|---|
| 30 | 0.103 | 2.40 |
| 50 | 0.112 | 2.25 |

[a] First-order rate constant at 25.0°, determined by following formation of 2,4-dinitrophenoxide ion.

## Results

**Kinetics.** The first-order rate constants (sec$^{-1}$) for hydrolysis of these dinitrophenyl phosphates are given in Tables II–X and are plotted against pH, or hydrogen

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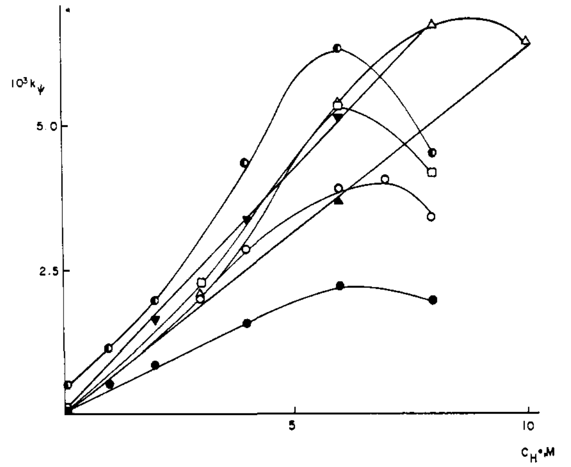

Figure 2. Acid hydrolyses at 73.0°: ●, 2,5-dinitrophenyl phosphate in $HClO_4$; ◐, 2,6-dinitrophenyl phosphate in $HClO_4$; ○, 2,4-dinitrophenyl phosphate in $HClO_4$; □, 2,4-dinitrophenyl phosphate in $H_2SO_4$; △, 2,4-dinitrophenyl phosphate in HCl; ▼, 2,4-dinitrophenyl phosphate in HCl + LiCl, $I = 8.0$; ▲, 2,4-dinitrophenyl phosphate in HCl + LiCl, $I = 10.0$.

or hydroxide concentration, in Figures 2–5. Unless specified, the solvent is water. Some results for *p*-nitrophenyl phosphate[3] are included for purpose of comparison in Tables II and V.

**Table II.** Acid Hydrolysis of *p*-Nitrophenyl and 2,4-Dinitrophenyl Phosphate[a]

| $C_{acid}$, *M* | 2,4-Dinitro |  |  |  |  |
|---|---|---|---|---|---|
|  | HCl | $H_2SO_4$ | $HClO_4$ |  | *p*-Nitro[c] |
| 0.01 |  |  | 0.13 | $0.37 \times 10^{-3\,b}$ | 0.042 |
| 0.10 |  |  | 0.17 | $1.05 \times 10^{-3\,b}$ | 0.038 |
| 1.00 |  |  | 0.54 | $5.45 \times 10^{-3\,b}$ | 0.086 |
| 3.00 | 2.09 | 2.25 | 2.02 | $21.7 \times 10^{-3\,b}$ | 0.140 |
| 4.00 |  |  | 2.84 | $33.0 \times 10^{-3\,b}$ | 0.153 |
| 6.00 | 5.35 | 5.32 | 3.90 | $55.8 \times 10^{-3\,b}$ | 0.092 |
| 7.00 |  |  | 4.04 |  | 0.029 |
| 8.00 | 6.67 | 4.15 | 3.39 | $51.2 \times 10^{-3\,b}$ | 0.025 |
| 10.00 | 6.37 |  |  |  |  |

[a] At 73.0° unless specified; values of $10^3k_\psi$, $sec^{-1}$. [b] At 25.0°. [c] In $HClO_4$, ref 3.

**Table III.** Acid Hydrolysis of 2,4-Dinitrophenyl Phosphate at 73.0° at Constant Ionic Strength

|  |  |  |  |  |  |
|---|---|---|---|---|---|
|  | $C_{HCl} + C_{LiCl} = 8.00\ M$ |  |  |  |  |
| $C_{HCl}$ | 0.10 | 2.00 | 4.00 | 6.00 | 8.00 |
| $10^3k_\psi$, $sec^{-1}$ | 0.18 | 1.64 | 3.37 | 5.08 | 6.67 |
|  | $C_{HCl} + C_{LiCl} = 10.00\ M$ |  |  |  |  |
| $C_{HCl}$ | 6.00 | 10.00 |  |  |  |
| $10^3k_\psi$, $sec^{-1}$ | 3.69 | 6.37 |  |  |  |

**Table IV.** Acid Hydrolysis of 2,5- and 2,6-Dinitrophenyl Phosphate[a]

| $C_{HClO_4}$, *M* | $10^3k_\psi$, $sec^{-1}$ 2,5 | 2,6 |
|---|---|---|
| 0.10 | 0.076 | 0.535 |
| 1.00 |  | 1.16 |
| 2.00 | 0.835 | 1.95 |
| 4.00 | 1.56 | 4.36 |
| 6.00 | 2.20 | 6.30 |
| 8.00 | 1.93 | 4.49 |

[a] At 73.0°.

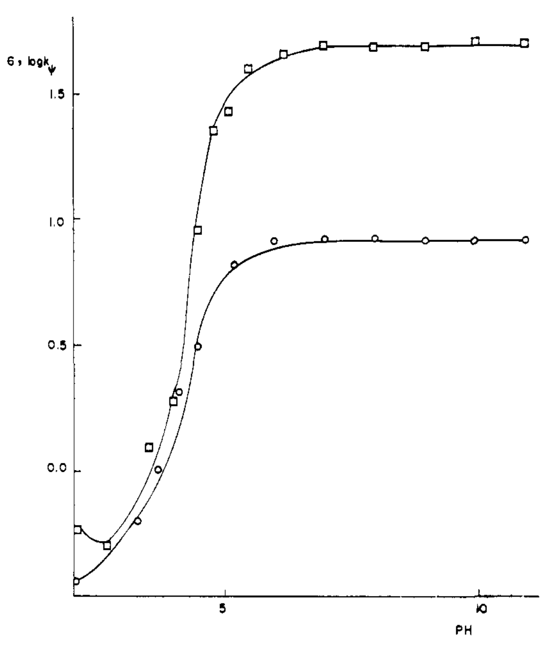

Figure 3. Variation of log $k_\psi$ with pH for the hydrolyses of 2,4- and 2,6-dinitrophenyl phosphates at 25.0°.

The acid hydrolyses show rate maxima in moderately concentrated acid, as is typical for hydrolysis of nitrophenyl phosphates, and these rate maxima may disappear if the ionic strength is kept constant[3] (Tables II–IV and Figure 2). The rate minima at pH 1–2, where the predominant species is the undissociated

**Table V.** Hydrolysis of *p*-Nitrophenyl and 2,4-Dinitrophenyl Phosphate

| pH | Buffer | $10^6k_\psi$,[a] 25.0° | $10^3k_\psi$,[a] 73.0° | $10^3k_\psi$,[b] 73.0° |
|---|---|---|---|---|
| 0.00 | $HClO_4$ | 5.45 |  |  |
| 1.00 | $HClO_4$ | 1.05 | 0.172 |  |
| 2.00 | $HClO_4$ | 0.368 | 0.132 | 0.043 |
| 3.30 | 0.01 *M* $KHC_8H_4O_4$ | 0.632 |  | 0.066 |
| 3.30 | 0.05 *M* |  | 0.287 |  |
| 3.70 | 0.05 *M* |  | 0.626 | 0.069 |
| 3.70 | 0.01 *M* | 1.02 |  |  |
| 4.01 | 0.01 *M* | 1.60[c] |  |  |
| 4.01 | 0.05 *M* | 2.31 | 1.12 | 0.063 |
| 4.10 | 0.01 *M* | 2.07 |  |  |
| 4.30 | 0.01 *M* | 2.50[c] |  |  |
| 4.30 | 0.05 *M* | 4.00 | 1.58 | 0.057 |
| 4.50 | 0.05 *M* | 5.98 | 2.68 |  |
| 4.50 | 0.01 *M* | 3.14 |  |  |
| 4.80 | 0.01 *M* | 4.77 |  |  |
| 5.00 | 0.01 *M* | 6.05[c] |  |  |
| 5.00 | 0.05 *M* | 7.81 | 3.60 |  |
| 5.20 | 0.05 *M* | 6.60 |  |  |
| 5.50 | 0.01 *M* | 7.31 |  | 0.0311 |
| 5.50 | 0.05 *M* | 9.48 | 4.23 |  |
| 5.90 | 0.05 *M* |  | 4.54 |  |
| 6.00 | 0.01 *M* $KH_2PO_4$ | 8.28 |  |  |
| 6.00 | 0.01 *M* |  | 4.83 |  |
| 6.50 | 0.01 *M* |  | 4.62 |  |
| 7.00 | 0.01 *M* | 8.39 | 5.01 |  |
| 7.50 | 0.05 *M* |  | 4.99 |  |
| 7.50 | 0.015 *M* $Na_2B_4O_7$ | 8.36 | 4.86 |  |
| 9.00 | 0.015 *M* | 8.28 | 4.80 |  |
| 10.00 | 0.015 *M* | 8.21 | 5.10 |  |
| 11.00 | 0.01 *M* $Na_2HPO_4$ | 8.21 | 5.15 |  |
| 12.00 | 0.01 *M* | 8.11 | 4.95 |  |

[a] 2,4-Dinitrophenyl phosphate. [b] *p*-Nitrophenyl phosphate, ref 3. [c] Interpolated values.

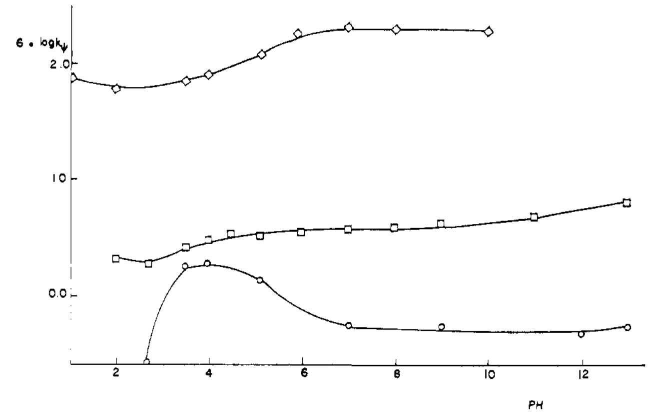

Figure 4. Variation of log $k_\psi$ with pH for the hydrolysis of 2,5-dinitrophenyl phosphate: O, at 25.0°; □, at 45.0°; and ◇, at 73.0°.

aryl phosphate, show that this species does not contribute appreciably to the hydrolysis, as for *p*-nitrophenyl phosphate, except at low temperature.[3,12]

Hydrolyses of the monoanions are relatively unimportant (Tables V–VII and Figures 3 and 4), except for 2,5-dinitrophenyl phosphate, where at 25° we observe the rate maximum at pH ~4 which is so characteristic of a readily hydrolyzable monoanion.[5]

**Table VI.** Hydrolysis of 2,6-Dinitrophenyl Phosphate

| pH | Buffer[a] | $10^6k_\psi$, $sec^{-1}$ 25.0° | 50.0° |
|---|---|---|---|
| 1.00 | HCl | 0.186 | |
| 2.00 | HCl | 0.057 | |
| 2.70 | $KH_2PO_4$ | 0.050 | |
| 3.50 | $KHC_8H_4O_4$ | 0.122 | |
| 4.00 | $KHC_8H_4O_4$ | 0.185 | |
| 4.50 | $KHC_8H_4O_4$ | 0.958 | |
| 4.80 | $KHC_8H_4O_4$ | 2.25 | |
| 5.10 | NaOAc | 2.67 | |
| 5.50 | $KHC_8H_4O_4$ | 3.97 | |
| 6.20 | $KH_2PO_4$ | 4.53 | 142 |
| 7.00 | $KH_2PO_4$ | 4.93 | |
| 8.00 | $Na_2B_4O_7$ | 4.88 | |
| 9.00 | $Na_2B_4O_7$ | 4.88 | 154 |
| 10.00 | $Na_2B_4O_7$ | 5.09 | 147 |
| 11.00 | $Na_2HPO_4$ | 4.97 | |
| 12.00 | $Na_2HPO_4$ | 5.02 | 153 |

[a] 0.01 *M*, pH 2.0–12.0.

**Table VII.** Hydrolysis of 2,5-Dinitrophenyl Phosphate

| pH | Buffer[a] | $10^6k_\psi$, $sec^{-1}$ 25.0° | 45.0° | 73.0° |
|---|---|---|---|---|
| 1.00 | $HClO_4$ | | | 76.0 |
| 2.00 | HCl | | 2.04 | 59.5 |
| 2.70 | $KH_2PO_4$ | 0.25 | 1.96 | |
| 3.50 | $KHC_8H_4O_4$ | 1.80 | 2.55 | 67.5 |
| 4.00 | $KHC_8H_4O_4$ | 1.83 | 2.96 | 78.0 |
| 4.50 | $KHC_8H_4O_4$ | | 3.24 | |
| 5.10 | NaOAc | 1.27 | 3.13 | 115 |
| 5.90 | $KHC_8H_4O_4$ | | | 169 |
| 6.00 | $KH_2PO_4$ | | 3.34 | |
| 7.00 | $KH_2PO_4$ | 0.53 | 3.60 | 195 |
| 8.00 | $Na_2B_4O_7$ | | 3.66 | 190 |
| 9.00 | $Na_2HPO_4$ | 0.54 | 4.03 | |
| 10.00 | $Na_2B_4O_7$ | | | 183 |
| 12.00 | $Na_2B_4O_7$ | 0.46 | | |

[a] 0.01 *M* buffer from pH 2.7 to 12.0.

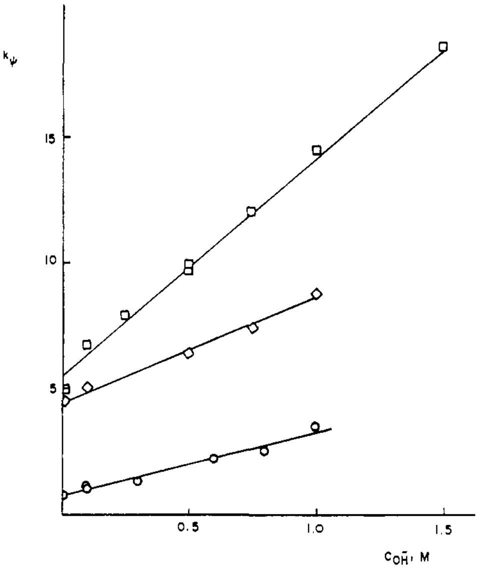

Figure 5. Variation of $k_\psi$ with $C_{OH^-}$ for the hydrolyses of 2,4-, 2,5-, and 2,6-dinitrophenyl phosphates at 25.0°. $10^5k_\psi$, $sec^{-1}$, for 2,4-dinitrophenyl phosphate, O; for 2,6-dinitrophenyl phosphate, □; $10^7k_\psi$, $sec^{-1}$, for 2,5-dinitrophenyl phosphate, ◇.

The dominant feature of the hydrolyses of these dinitrophenyl phosphates is the constant reaction rate between pH 6 and 12 (Tables V–VII and Figures 3 and 4), except for the 2,5-dinitro compound where the form of the rate–pH profile depends on temperature (Table VII and Figure 4). It should be possible to observe a rate constant which is independent of pH over a wide range by working at a temperature close to 35°.

**Table VIII.** Alkaline Hydrolyses in Water[a]

| Substrate | Dinitrophenyl phosphates | | | | | |
|---|---|---|---|---|---|---|
| $C_{NaOH}$, | 2,4 | | 2,5 | | 2,6 | |
| *M* | 25.0° | 73.0° | 25.0° | 45.0° | 25.0° | 50.0° |
| 0.10 | 1.04 | 376[b,c] | 0.051 | 0.577 | 6.83 | 171 |
| 0.25 | | | | | 7.97 | 217 |
| 0.30 | 1.36 | | | | | |
| 0.50 | 1.90 | 538 | 0.065 | 1.04 | 9.73 | 285 |
| 0.60 | 2.24 | | | | | |
| 0.75 | | | 0.074 | | 12.1 | |
| 0.80 | 2.51 | | | | | |
| 1.00 | 3.50 | 606 | 0.088 | 1.62 | 14.6 | |
| 1.00 | 2.95[d] | | | | | |
| 1.00 | 4.72[e] | | | | | |

[a] Values of $10^5k$ in $sec^{-1}$. [b] In 0.1 *M* KCl. [c] In 0.1 *M* NaOH at 73.0° for *p*-nitrophenyl phosphate[3] $10^5k_\psi = 0.21$ $sec^{-1}$. [d] LiOH. [e] KOH.

**Table IX.** Salt Effects on the Dianion Hydrolysis of 2,4-Dinitrophenyl Phosphate[a]

| Salt | $C_{salt}$, *M* | $10^5k_\psi$, $sec^{-1}$ |
|---|---|---|
| ... | ... | 0.83 |
| LiCl | 0.50 | 1.44 |
| NaCl | 0.50 | 1.42 |
| NaCl | 1.00 | 1.80 |
| KCl | 0.50 | 1.74 |
| $NaClO_4$ | 0.50 | 1.61 |
| $Na_2SO_4$ | 0.25 | 1.54 |

[a] In water at 25.0° in 0.015 *M* $Na_2B_4O_7$ buffer, pH maintained at 9.00.

Table X. Salt Effects on the Hydrolysis of 2,4-Dinitrophenyl Phosphate at High pH[a]

| $C_{NaOH}$, $M$ | Salt | $C_{salt}$, $M$ | $10^5k_\psi$, sec$^{-1}$ |
|---|---|---|---|
| 0.10 | ... | ... | 1.04 |
| 0.10 | NaCl | 0.90 | 2.23 |
| 0.10 | NaBr | 0.90 | 2.06 |
| 0.10 | $NaClO_4$ | 0.90 | 1.92 |
| 0.10 | $Na_2SO_4$ | 0.45 | 2.16 |
| 0.50 | ... | ... | 1.90 |
| 0.50 | NaCl | 0.50 | 2.89 |
| 1.00 | ... | ... | 3.50 |

[a] In water at 25.0°.

Table XI. Solvolyses of 2,4- and 2,6-Dinitrophenyl Phosphate in Aqueous Alcohol[a]

| | | | 2,4-Dinitro | | 2,6-Dinitro | |
|---|---|---|---|---|---|---|
| Alcohol | $ROH:H_2O$, v/v | [ROH], mole % | $10^5k_\psi$, sec$^{-1}$ | $ROPO_3H_2$, mole % | $10^5k_\psi$, sec$^{-1}$ | $ROPO_3H_2$, mole % |
| Methanol | 30:70 | 15.5 | 1.77,[b] 1.67[c] | 52 | 7.50,[b] 7.76[c] | 67 |
| Methanol | 50:50 | 29.2 | 3.28,[b] 3.08[c] | 67 | 5.00,[b] 4.80[c] | 83 |
| Methanol | 60:40 | 40.2 | 4.36,[b] 4.45[c] | 88 | 3.84,[b] 4.32[c] | 88 |
| Ethanol | 30:70 | 11.3 | 1.81,[b] 1.95[c] | 31 | | |
| Ethanol | 40.5:59.5 | 17.4 | 3.02,[b] 2.98[c] | 31 | | |
| Ethanol | 50:50 | 22.4 | 3.78,[b] 3.70[c] | 37 | | |
| Ethanol | 57.2:42.8 | 29.2 | 5.65,[b] 5.63[c] | 45 | | |

[a] At 25.0°, with 0.15 $M$ $Na_2B_4O_7$, pH 8.0 in water. [b] Following dinitrophenol. [c] Following inorganic phosphate.[21]

Table XII. Alkaline Methanolysis of 2,4-Dinitrophenyl Phosphate at 25.0°

| $C_{NaOCH_3}$, $M$ | $10^4k_\psi$, sec$^{-1}$ | ArOH, mole % | ArOH/ $ArOCH_3$ |
|---|---|---|---|
| 0.05 | 2.30[a] | 46.3 | 0.87[d] |
| 0.10 | 3.70[a] | 42.3 | 0.73[d] |
| 0.10 | 3.78[b] | 40.1 | 0.67[e] |
| 0.10 | 3.82[c] | | |
| 0.30 | 8.90[a] | 35.8 | 0.56[d] |
| 0.41 | 11.5[a] | 31.2 | 0.45[d] |

[a] Following 2,4-dinitrophenoxide ion at 3580 A. [b] Following 2,4-dinitroanisole at 2920 A. [c] Following inorganic phosphate.[21] [d] Calculated by measuring optical densities before and after hydrolysis of the products. [e] By measuring 2,4-dinitrophenoxide ion and inorganic phosphate.[21]

Table XIII. Alkaline Methanolysis of 2,6-Dinitrophenyl Phosphate at 25.0°

| $C_{NaOCH_3}$, $M$ | $10^4k_\psi$, sec$^{-1}$ | ArOH,[c] mole % | ArOH/ $ArOCH_3$ |
|---|---|---|---|
| 0.05 | 0.59[a] | 14.2 | 0.166 |
| 0.10 | 2.20[a] | 9.7 | 0.107 |
| 0.30 | 10.0[b] | 7.4 | 0.080 |
| 0.30 | 10.1[a] | 7.6 | 0.082 |
| 0.41 | 14.0[a] | 7.2 | 0.078 |

[a] Following 2,6-dinitrophenoxide at 4290 A. [b] Following 2,6-dinitroanisole at 3580 A. [c] Calculated by measuring optical densities before and after hydrolysis of the products.

Table XIV. Formation of 2,4-Dinitrophenol from 2,4-Dinitrophosphoryl Dichloride

| pH | $KHC_8H_4O_2$ buffer, $M$ | $10^6k_\psi$, sec$^{-1}$ 25.0° | $10^3k_\psi$, sec$^{-1}$ 73.0° |
|---|---|---|---|
| 3.30 | 0.05 | 0.632 | 3.09 |
| 3.30 | 0.10 | 0.802 | |
| 3.70 | 0.10 | 1.26 | |
| 4.01 | 0.10 | 2.25 | |
| 4.01 | 0.05 | 2.13 | 9.80 |
| 4.50 | 0.05 | 5.77 | 24.1 |

Small changes in the buffer concentration from 0.01 to 0.05 $M$ affect the reaction rate in the pH region 5–7 where the ionic species of the phosphate is changing from mono- to dianion (Table V). Changes in buffer concentration are less important in the "plateau" region pH 7–12, as shown by the results of 73°. In order to minimize these problems we used 0.01 or 0.015 $M$ concentrations over a wide pH range, and the figures are plotted using the results of these experiments where possible, and the Arrhenius parameters were calculated from them. However, addition of high concentrations of electrolyte does affect the rate, even in the "plateau" region (Table IX).

At pH 12, $k_\psi$ increases with hydroxide ion concentration (Table VIII and Figure 5). Again added salts increase the rate (Table X).

Addition of ethanol or methanol initially increases the rate of the "dianion" reactions of the 2,4 and 2,6 compounds (Table XI), and methoxide is more reactive than hydroxide ion (Tables XII and XIII).

The first-order rate constants for release of 2,4-dinitrophenol from the aryl phosphate and the aryl phosphoryl dichloride are very similar (Tables V and XIV), suggesting that the dichloride is hydrolyzed very rapidly to the phosphate, which then slowly decomposes.

$$(NO_2)_2C_6H_3OPOCl_2 \longrightarrow (NO_2)_2C_6H_3OPO_3^{2-} \longrightarrow (NO_2)_2C_6H_3O^-$$

**Arrhenius Parameters.** The variation of rate of the acid hydrolysis with temperature was examined only for 2,4-dinitrophenyl phosphate, and in 6 $M$ perchloric acid $E$ = 18 kcal/mole and log $A$ = 9.0, giving $\Delta S^{\ddagger} = -23$ eu (calculated for 1 $M$ acid at 25°). For hydrolyses of the dianions the corresponding values are activation energies: 2,4-, 25.5; 2,5-, 28; and 2,6-, 26 kcal/mole; activation entropies: 2,4-, +2.5; 2,5-, +1; and 2,6-, +6.5 eu.

**Products.** Solvolyses of 2,4- and 2,6-dinitrophenyl phosphates in aqueous methanol or ethanol give phenol and alkyl or inorganic phosphate at pH ~8 where the dianion is the reactive species (Table XI). The absence of dinitroanisole is consistent with a reaction involving only phosphorus–oxygen bond fission.

In strongly alkaline methanol both dinitroanisole and phenol are formed (Tables XII and XIII), showing that reaction involves both carbon and phosphorus–oxygen bond fission.

## Discussion

**Hydrolysis in Strong Acid.** As in the acid hydrolyses of $p$-acetyl and $p$-nitrophenyl phosphates, the cata-

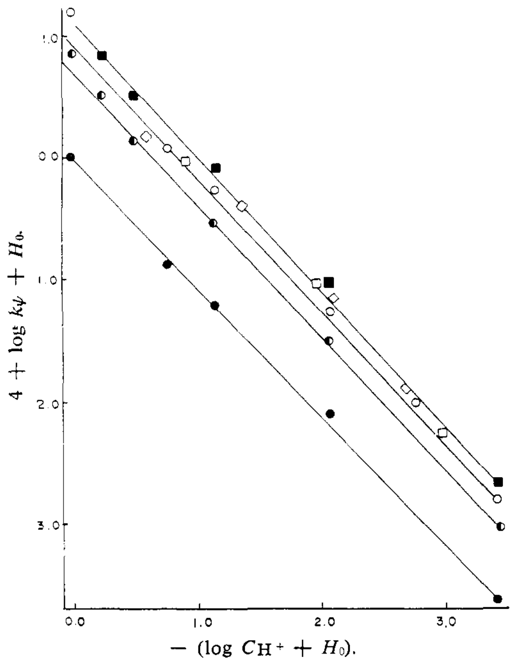

Figure 6. Plot of $\log k_\psi + H_0$ against $-(\log C_{H^+} + H_0)$: ◇, 2,4-dinitrophenyl phosphate at 73.0° in HCl; □, 2,4-dinitrophenyl phosphate at 73.0° in $H_2SO_4$; ○, 2,4-dinitrophenyl phosphate at 73.0° in $HClO_4$; ●, 2,4-dinitrophenyl phosphate at 25.0° in $HClO_4$; ◐, 2,5-dinitrophenyl phosphate at 73.0° in $HClO_4$; ■, 2,6-dinitrophenyl phosphate at 73.0° in $HClO_4$.

lytic effectiveness of the acids is HCl > $H_2SO_4$ > $HClO_4$.[3] This order does not depend upon the different nucleophilicities of the anions of the acids because the rate is decreased by addition of chloride ions (Table III and Figure 2).

Bunnett has put forward relations between reaction rate and water activity, and for many reactions, plots of $\log k_\psi + H_0$, or $\log k_\psi - \log c_{H^+}$, *vs.* $\log a_{H_2O}$ are linear, and he has suggested that $w$ and $w^*$, the slopes of these plots, give evidence of reaction mechanism.[26] For the acid hydrolysis of *p*-nitrophenyl phosphate, approximately linear plots were obtained for hydrochloric, sulfuric, and perchloric acids, and $w$ was ~7 and $w^*$ was ~2, but the treatment failed for hydrolyses in toluene-*p*-sulfonic acid and in mixtures of hydrochloric acid and lithium chloride[3] and it is improbable that the hydrolyses involved slow proton transfers, as might be indicated by the $w$ and $w^*$ values.[26] The acid hydrolysis of these dinitrophenyl phosphates shows this same high dependence of rate upon water activity, with $w$ and $w^*$ *ca.* 7 and 2, respectively. Bunnett and Olsen have recently suggested a modification of the original treatment in which they plot $\log k_\psi + H_0$ against $H_0 + \log C_{H^+}$, and the slope, $\phi$, is a parameter which indicates the effect of activity upon reaction rate.[27] As shown in Figure 6 the points for the acid hydrolyses of the three dinitrophenyl phosphates fit this relationship giving parallel straight lines, even for different acids and temperatures. The value of $\phi$ is ~1.2, consistent with a high dependence of reaction rate upon water activity.[27]

As was found for *p*-nitrophenyl phosphate,[3] the maximum disappears if the electrolyte concentration is kept constant (Figure 2). Mixtures of lithium and hydrogen chloride are especially effective for this purpose because the lithium and hydronium ions have similar partial molar volumes and affect the water activity similarly.[28]

These rate maxima have a different origin from those caused by complete protonation of the substrate,[3,26,29] and for the acid hydrolysis of *p*-nitrophenyl phosphate isotopic evidence shows that the rate maxima is not associated with hydration equilibria followed by slow proton transfers,[3] although Martin has shown how such mechanisms could lead to rate maxima in acid.[30]

Many acid hydrolyses are insensitive to the electronic effects of substituents because substituents which increase the basicity of the substrate also inhibit nucleophilic attack by the solvent.[31] Simple monoaryl phosphates show no acid-catalyzed hydrolysis, and it is difficult to understand how nitro or acetyl substituents could promote an acid-catalyzed hydrolysis of monoaryl phosphates unless they interact strongly with the acidic solvent, and in contrast to the usual behavior,[31] the rate of hydrolysis in acid increases with increasing electron withdrawal by the nitro groups, as is shown by the following values for the first-order rate constants at the rate maximum in perchloric acid at 73°: *m*-nitro,[32] $4.6 \times 10^{-5}$; *p*-nitro,[3] $1.5 \times 10^{-4}$; *o*-nitro,[32] $2.5 \times 10^{-4}$; 2,5-dinitro, $2.2 \times 10^{-3}$; 2,4-dinitro-, $4.0 \times 10^{-3}$; and 2,6-dinitro, $6.3 \times 10^{-3}$ $sec^{-1}$.

A plot of $\log k_\psi$, at its maximum, against p$K$ of the phenol is linear, with some scatter for the *o*-nitro compounds, and with a slope of ~0.5. Therefore, the acid hydrolysis is more sensitive to electron-withdrawing substituents than is the monoanion reaction where the corresponding slope is ~0.3,[32] but less sensitive than the dianion reaction where it is ~1.7 (Tables V–VII).

These rate maxima occur only in those acid hydrolyses which involve attack of water upon an unsaturated electrophilic center, as in hydrolyses of fluorocarboxylic esters,[33] *o*-dinitrophenyl oxalate,[34] *o*-phenylene sulfite,[35] and some carboxylic anhydrides.[36] These reactions have low activation energies and negative activation entropies, suggesting that the transition state is much more hydrated than the initial state, in agreement with Bunnett's conclusions.[26,27]

**Hydrolysis at pH 1–12.** For most monoalkyl and aryl phosphates the monoanion is especially reactive in hydrolysis.[5,9,37]

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[26] J. F. Bunnett, *J. Am. Chem. Soc.*, **83**, 4956 (1961), and accompanying papers.

[27] J. F. Bunnett and F. P. Olsen, *Can. J. Chem.*, in press.

[28] R. A. Robinson and R. H. Stokes, "Electrolyte Solutions," Butterworth and Co., Ltd., London, 1959, Appendix.

[29] D. Rosenthal and T. I. Taylor, *J. Am. Chem. Soc.*, **79**, 2684 (1957); S. Marburg and W. P. Jencks, *ibid.*, **84**, 232 (1962); J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 2000 (1957).

[30] R. B. Martin, *J. Am. Chem. Soc.*, **84**, 4130 (1962).

[31] C. K. Ingold, *J. Chem. Soc.*, 1032 (1930); R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chapter 13.

[32] E. J. Fendler, Ph.D. Thesis, University of California, Santa Barbara, 1966.

[33] C. A. Bunton and T. Hadwick, *J. Chem. Soc.*, 3248 (1958); 943 (1961).

[34] M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Am. Chem. Soc.*, **80**, 5380 (1958).

[35] J. G. Tillett, *J. Chem. Soc.*, 5138 (1960); C. A. Bunton and G. Schwerin, *J. Org. Chem.*, **31**, 842 (1966).

[36] C. A. Bunton, J. H. Fendler, N. A. Fuller, S. Perry, and J. Rocek, *J. Chem. Soc.*, 6174 (1965).

[37] W. W. Butcher and F. H. Westheimer, *J. Am. Chem. Soc.*, **77** 2420 (1955).

For a large number of monalkyl and aryl phosphates, including those in the literature,[5] and *o*- and *m*-nitro-, *o*- and *p*-chloro-, and several alkylphenyl phosphates we find that a plot of log $k$, for monoanion hydrolysis at 100°, against p$K$ of the phenol is linear (provided that bulky *ortho* substituents and neighboring groups are absent), with slope of $\sim 0.3$.[32] From this relation we estimate that the approximate reactivities of the monoanions of the dinitrophenyl phosphates, relative to that of *p*-nitrophenyl phosphate, should be: 2,4-, 5.5; 2,5-, 3; and 2,6-, 7; and, therefore, at 73° the estimated first-order rate constants for the monoanion hydrolyses are: 2,4-, $4 \times 10^{-4}$; 2,5-, $2 \times 10^{-4}$; and 2,6-, $5 \times 10^{-4}$ sec$^{-1}$. For the 2,4- and 2,6-dinitrophenyl phosphates the actual, or extrapolated, rate constants at 73° and pH 2–3 where the monoanion would be the bulk species are greater than these values (Tables V and VI), whereas they are slightly smaller for the 2,5 isomer (Table VII). There is considerable uncertainty in these estimated rate constants for the (hypothetical) hydrolyses of the monoanions, but for the 2,4- and 2,6-dinitro compounds any monoanion hydrolysis should be masked by the dianion hydrolysis, but should be observable for 2,5-dinitrophenyl phosphate, as is found.

**Hydrolysis at pH 6–12.** With a few exceptions,[4–6] dianions of monoalkyl and monoaryl phosphates are unreactive but dianions of acyl phosphates are reactive.[8] Most alkoxy and aryloxy groups are poor leaving groups, and can separate from phosphorus only if a proton is transferred to them, from the phosphate itself, as in hydrolysis of the monoanions, or from a neighboring general acid.[4,5]

With a good leaving group, *e.g.*, carboxylate, proton transfer is not essential to reaction,[8] and a dinitrophenoxide anion should be able to leave without assistance from a neighboring hydroxyl group. The hydrolysis of *p*-nitrophenyl phosphate becomes faster as the pH is increased above pH 12,[3,7] but this reaction may involve both spontaneous hydrolysis of the dianion and attack of hydroxide ion upon it. For the dinitrophenyl phosphates the pH–rate profile above pH 6 can be interpreted most simply in terms of the dianion as the sole reactive species from pH 6 to 12.[17]

The line drawn for the hydrolysis of 2,4-dinitrophenyl phosphate between pH 3 and 11 in Figure 3 is that calculated on the assumption that the dianion is the only reactive species, and that for 2,4-dinitrophenyl phosphate the p$K$ values for the first and second acid dissociations are 1 and 4.5, respectively. (The fit is little dependent upon the choice of the first p$K$, although the value used is not unreasonable in view of values for other aryl phosphates.[3,12]) Over a wide pH range the kinetic form of the hydrolysis of 2,4- and presumably of 2,6-dinitrophenyl phosphate is

$$k_\psi = k_2[\mathrm{ArOPO_3}^{2-}]$$

At high pH there is an increase in rate which will be discussed subsequently.

However, the kinetic form of the hydrolysis from pH 6 to 12 could arise from attack of hydroxide ion upon the monoanion.

$$\mathrm{ArOPO_3H^-} + \mathrm{OH^-} \longrightarrow \mathrm{ArOH} + \mathrm{HOPO_3}^{2-}$$

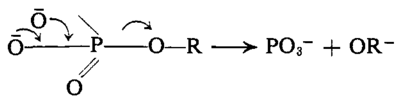
Such a reaction is not unreasonable because lyate ions can attack the dianion. Di Sabato and Jencks considered this problem with respect to the hydrolysis of acyl phosphates and concluded that attack of hydroxide ion upon the monoanion did not occur.[8] Their evidence was based largely on kinetic studies, although the position of bond fission was consistent with their mechanism. Arguments based on the entropy and volume of activation deserve special consideration in phosphate reactions. For reaction between hydroxide ion and the monoanion the rate equation would be

$$v = k_2' \frac{K_w}{K_2}[\mathrm{ROPO_3}^{2-}]$$

(where $k_2'$ is the second-order rate constant for attack of hydroxide ion upon the monoanion, and $K_2$ is the second acid dissociation constant; activity effects are neglected).

For reaction between hydroxide ion and monoanion the entropy of activation and the volume of activation should be negative; however we must also consider the acid–base equilibria involving ionization of water and the phosphate monoanion. The second dissociation constants for aryl phosphates are not known sufficiently accurately over a temperature range to allow the calculation of entropies of ionization, but for ionization of the dihydrogen phosphate monoanion in water $\Delta S^\circ = -30$ eu, and for the autoprotolysis of water it is $-18.7$ eu.[38] If the entropies of ionization of monoanions of aryl phosphates are similar to that of dihydrogen phosphate monoanion, the difference between them and the entropy of ionization of water would make a large positive contribution to the observed activation entropy for the hypothetical reaction between hydroxide ion and organic phosphate monoanion at the constant pH. For a number of reasons one must be cautious in using volumes of activation as mechanistic criteria for ionic reactions in which there are acid–base equilibria involving multicharged ions (*cf.* ref 39).

However, a reaction between a dinitrophenyl phosphate monoanion and hydroxide ion would have to have a second-order rate constant of *ca.* $2 \times 10^4$ l. mole$^{-1}$ sec$^{-1}$, and it seems that the results can be interpreted most simply in terms of a dianion heterolysis, with the two negative charges providing considerable driving force, although it is improbable that monomeric metaphosphate ion becomes completely free in the reaction.



The pH–rate profile of the hydrolysis of 2,5-dinitrophenyl phosphate changes with increasing temperature from that corresponding to heterolysis of the monoanion with its associated rate maximum to a plateau, showing that for this compound hydrolysis of the dianion has a higher activation energy than that of the monoanion. Such an energetic difference is reasonable because in the monoanion heterolysis departure of the aryloxy group is assisted by protonation.

The hydrolyses of the mono- and dianions of 2,5-dinitrophenyl phosphates must have similar rates at the

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(38) H. S. Harned and B. B. Owen, "Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold Publishing Corp., New York, N. Y., 1958, p 667.

(39) E. Whalley, *Advan. Phys. Org. Chem.*, 2, 93 (1964).

temperatures at which we are working, and because the dianion hydrolysis has the higher activation energy, it must also have a more positive entropy of activation than the monoanion hydrolysis. Proton transfer appears to be essential for monoanion heterolysis,[5] and whether it occurs directly or through water molecules will involve some ordering in the transition state. There is no such restriction in heterolysis of the dianion, and dispersion of the negative charges in the transition state should decrease solvation and release of water molecules should increase the entropy of the system during its formation.

Although we found a rate maximum in the hydrolysis of 2,5-dinitrophenyl phosphate at pH 4 by working at a low temperature, we did not observe the smooth bell-shaped curve which is so typical of the hydrolyses of most simple monosubstituted phosphates.[3,5,9,37] There is a marked "tail" on the high pH side of the maximum, even at 25°, suggesting that at pH 4.5–6 there is a contribution of the dianion reaction, and this conclusion is confirmed by the appreciable constant rate of hydrolysis from pH 7 to 12 (Figure 4).

**Salt Effects on the Hydrolysis of the Dianion.** Added salts increase the rate of hydrolysis of the dianion (Table IX). The effect is specific, and depends more upon the cation than the anion. Sodium chloride, perchlorate, and sulfate increase $k_\psi$ by similar amounts, but potassium chloride has a bigger effect.

Kirby and Varvoglis report a rate constant for the dianion hydrolysis corresponding to $170 \times 10^{-6}$ sec$^{-1}$ in 1 $M$ potassium chloride at 39°[17] whereas our interpolated value is $57 \times 10^{-6}$ sec$^{-1}$ at 39°. Much of this difference could be due to the ionic strength effect of the potassium chloride.

The apparent importance of cationic size suggests that the cation may interact closely with the aryl phosphate dianion, although such interactions at first sight seem improbable in water. The specificity of these salt effects shows that there is little point in trying to eliminate complications caused by salt effects by addition of large amounts of added electrolyte, or by working at some fixed ionic strength.

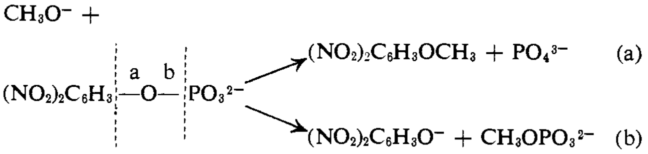
**Reaction at High pH.** Addition of hydroxide ion increases the rate of hydrolysis. An alkali metal hydroxide may have an electrolyte effect upon the dianion hydrolysis, just as do other electrolytes (Table IX), but unless this effect is unexpectedly large it would be insufficient to explain the rate enhancement by added alkali. Although there is usually a logarithmic relation between rate constant and electrolyte concentration,[40] for small rate effects it is indistinguishable from a linear relation. The kinetic form is

$$k_\psi = k_2 + k_3 C_{\mathrm{OH}^-}$$

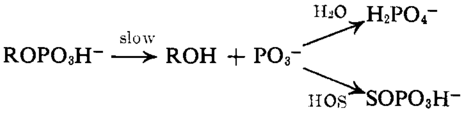
(Figure 3 and Table VIII). The hydroxide ion dependent term could include contributions due to attack of hydroxide ion upon carbon and phosphorus, as well as an electrolyte effect. The term $k_3$ is more dependent upon the acidity of the phenol than is $k_2$, as would be expected for nucleophilic attack upon a dianion.

The effect of cations upon the reaction rate is shown by the greater rate in potassium as compared with sodium or lithium hydroxide (Table VIII), and there are positive specific salt effects upon the reaction rate at high pH (Table X) which also depend markedly upon the nature of the cation.

We have assumed that the spontaneous hydrolysis of the dianion occurs with elimination of metaphosphate ion, and solvolysis of the dianion in aqueous methanol or ethanol gives no dinitroanisoles (Results), suggesting that only phosphorus–oxygen fission is involved in these reactions, whereas reactions at high pH in alkaline methanol give 2,4- and 2,6-dinitroanisole (Table XII) by attack of methoxide ion upon the dinitrophenyl residue (a), as well as phenol probably by attack upon phosphorus (b) and by spontaneous dianion heterolysis.


$$CH_3O^- + (NO_2)_2C_6H_3 \overset{a}{\vdots} O \overset{b}{\vdots} PO_3^{2-} \begin{cases} \rightarrow (NO_2)_2C_6H_3OCH_3 + PO_4^{3-} & \text{(a)} \\ \rightarrow (NO_2)_2C_6H_3O^- + CH_3OPO_3^{2-} & \text{(b)} \end{cases}$$

**Solvolysis in Aqueous and Absolute Alcohols.** It is generally assumed that hydrolysis of the monoanions of phosphate esters occurs by elimination of the (hypothetical) metaphosphate ion. Some of the evidence for this mechanism is that the rate of several solvolyses of phosphate monoanions is little affected by addition to water, but that the product is changed.[5,41] The simplest explanation of these results is that alcohols and water have similar reactivities toward a metaphosphate ion whose fate does not depend materially upon the nature of the organic residue.


$$ROPO_3H^- \xrightarrow{\text{slow}} ROH + PO_3^- \begin{cases} \xrightarrow{H_2O} H_2PO_4^- \\ \xrightarrow{HOS} SOPO_3H^- \end{cases}$$

This explanation is oversimplified because the (hypothetical) metaphosphate intermediates formed in solvolyses of pyrophosphate anions,[42] and deaminations of phosphoroamidate,[43] do not react indiscriminately with the components of an aqueous alcohol solvent, suggesting that they may not always become completely free before solvent capture, and for these reactions their fate may depend critically on the natures of their precursor, and of the solvent molecules about the reaction center. The solvent effects upon the rates and products of dianion solvolyses in aqueous alcohol are consistent with elimination of some form of metaphosphate ion which is captured preferentially by alcohol. The over-all rates of solvolysis of the dianions of 2,4- and 2,6-dinitrophenyl phosphates increase initially with addition of alcohol (Figure 7), but whereas they increase smoothly for the 2,4 compound there is a maximum at ~15 mole % methanol for the 2,6 compound, and the rate decreases sharply with increasing methanol content of the solvent.

The ability of an alcohol to trap the hypothetical metaphosphate ion depends not only upon the reaction mechanism, but also upon the organic residue; *e.g.*, for solvolysis of the dianions more methyl phosphate is

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(40) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," John Wiley and Sons, Inc., New York, N. Y., 1952, p 140.

(41) P. A. T. Swoboda and E. M. Crook, *Biochem. J.*, **59**, xxiv (1955); P. A. T. Swoboda, Special Publication No. 8, The Chemical Society, London, 1957, p 41; J. D. Chanley and E. Feageson, *J. Am. Chem. Soc.*, **85**, 1181 (1963).

(42) C. A. Bunton and H. Chaimovich, *Inorg. Chem.*, **4**, 1763 (1965).

(43) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **86**, 1410 (1964).

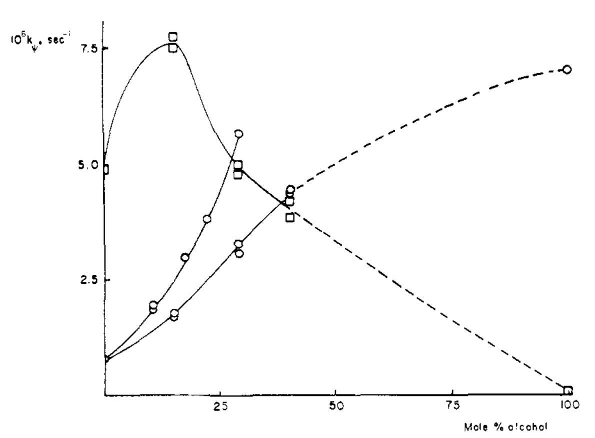

Figure 7. Solvent effect upon the dianion hydrolysis at 25.0°: ○, 2,4-dinitrophenyl phosphate in aqueous methanol; ●, 2,4-dinitrophenyl phosphate in aqueous ethanol; □, 2,6-dinitrophenyl phosphate in aqueous methanol. The solid line is drawn through points for rate constants which were measured directly.

formed from the 2,6- than from the 2,4-dinitrophenyl phosphate (Table XI). For 2,4-dinitrophenyl phosphate dianion, the approximate relative reactivities toward metaphosphate are: $CH_3OH$, 6; $C_2H_5OH$, 2; and $H_2O$, 1. (The value for the least aqueous methanol, where the experimental error is largest, gives a relative reactivity of methanol to water of 10.) For 2,6-dinitrophenyl phosphate dianion the reactivity of methanol, relative to water, is 11. For solvolysis of the monoanion of *p*-nitrophenyl phosphate, water and the alcohols have very similar reactivities toward metaphosphate ion,[41] and the differences in relative reactivities in the dianion reactions seem to depend upon the presence of *o*-nitro groups. Although ethanol is the most "reactive" of the solvents, at least in low concentration, so far as speeding the solvolysis of 2,4-dinitrophenyl phosphate is concerned, it is not the most effective solvent in trapping intermediate.

It would be difficult to accommodate these observations to a mechanism involving nucleophilic attack of the lyate ion upon the dinitrophenyl phosphate monoanion.

(1) In such a reaction there should be some attack of the alkoxide ion upon the phenyl group with formation of phenolic ether; none was observed.

(2) If reaction involved bimolecular attack of lyate ions upon the aryl phosphate monoanion there should be simple reactions between the reaction rates and products, and their absence suggests that the rate-limiting and product-forming steps are different.[41,44]

For solvolysis of the dianion of 2,4-dinitrophenyl phosphate and of the 2,6 compound in methanol of high water content, the kinetic solvent effect fits the qualitative solvent theory of Hughes and Ingold,[44] which predicts that a reaction in which a charge is dispersed, as in I, should be slightly accelerated by a decrease in the polarity of the solvent.

$$\text{ArO-PO}_3^{2-} \longrightarrow \underset{\text{I}}{[\text{ArO}^- \cdots \text{PO}_3^-]^{\ddagger}}$$

However, this theory has to be applied cautiously, because it ignores entropy effects.[44] Addition of alcohol to water slightly retards the solvolysis of the monoanion of *p*-nitrophenyl phosphate,[5,41] even though this reaction formally involves dispersion of an existing charge and the rates of hydrolysis of the mono- and dianions of acetyl phosphate are insensitive to the addition of acetonitrile.[8] The theory fails completely for the solvolysis of 2,6-dinitrophenyl phosphate dianion because the rate of solvolysis falls sharply when the methanol content is greater than 15 mole %.

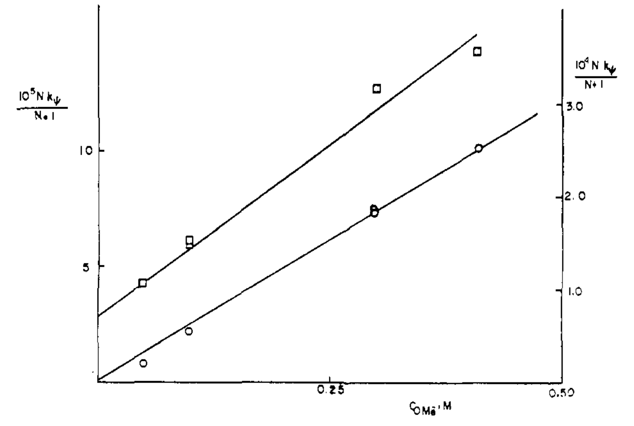

Figure 8. Plot of $k_\psi N/(N+1)$ against methoxide ion concentration in absolute methanol at 25.0°: □, 2,4-dinitrophenyl phosphate (right-hand scale); ○, 2,6-dinitrophenyl phosphate (left-hand scale).

Reaction in strongly alkaline solutions of methanol can give phenol and methyl phosphate by a spontaneous decomposition of the dianions

$$\text{ArO}\!-\!\vdots\,\text{PO}_3^{2-} \xrightarrow[\text{slow}]{k_2} \text{ArO}^- + \text{PO}_3^- \xrightarrow[\text{fast}]{\text{CH}_3\text{OH}} \text{CH}_3\text{OPO}_3\text{H}^-$$

or by nucleophilic attack upon phosphorus

$$\text{ArO}\!-\!\vdots\,\text{PO}_3^{2-} + \text{OCH}_3^- \xrightarrow{k_3^{\text{P}}} \text{ArO}^- + \text{CH}_3\text{OPO}_3^{2-}$$

and dinitroanisole and inorganic phosphate by nucleophilic attack upon the phenyl group.

$$\text{CH}_3\text{O}^- + \text{Ar}\,\vdots\!-\!\text{OPO}_3^{2-} \xrightarrow{k_3^{\text{C}}} \text{CH}_3\text{OAr} + \text{PO}_4^{3-}$$

Neglecting kinetic salt effects the observed first-order rate constant in methanol with respect to aryl phosphate is

$$k_\psi = k_2 + C_{\text{OCH}_3^-}(k_3^{\text{P}} + k_3^{\text{C}})$$

and the ratio, $N$, of dinitrophenol to dinitroanisole is

$$N = (k_2 + k_3^{\text{P}} C_{\text{OCH}_3^-})/k_3^{\text{C}} C_{\text{OCH}_3^-}$$

and therefore

$$k_\psi N/(N+1) = k_2 + k_3^{\text{P}} C_{\text{OCH}_3^-}$$

The plots of $k_\psi N/(N+1)$ against concentration of methoxide ion are shown in Figure 8. The intercept gives $k_2 = 7.0 \times 10^{-5}$ sec$^{-1}$, and the slope gives $k_3^{\text{P}} = 7.5 \times 10^{-4}$ l. mole$^{-1}$ sec$^{-1}$ and, therefore, $k_3^{\text{C}} = 22 \times 10^{-4}$ l. mole$^{-1}$ sec$^{-1}$ for decomposition of 2,4-dinitrophenyl phosphate dianion. The value of $k_2$ is very small, and $k_3^{\text{P}} = 2.5 \times 10^{-4}$ and $k_3^{\text{C}} = 3.2 \times 10^{-4}$ l. mole$^{-1}$ sec$^{-1}$, for decomposition of 2,6-dinitrophenyl phosphate dianion. Although a linear relation is obtained (Figure 8) there is uncertainty in the significance of $k_2$, $k_3^{\text{C}}$, and $k_3^{\text{P}}$, because the treatment assumes a second-order kinetic form for attack of methoxide ion, and that $k_2$ will be independent of methoxide ion.

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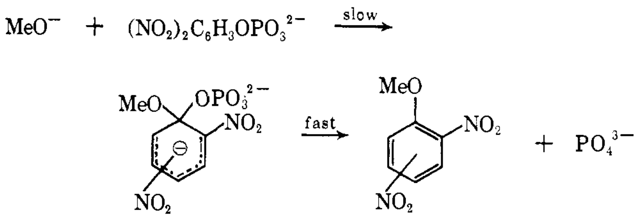
[44] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, Chapter VII.

For example, we cannot distinguish between a positive salt effect of the methoxide ion upon dianion solvolysis and attack of methoxide ion upon the phosphorus atom. This problem cannot be avoided by working at constant ionic strength, because kinetic salt effects depend upon the nature of the electrolyte.

Reactions of the dianions with alkoxide ion gives considerable amounts of ethers by nucleophilic attack upon the phenyl group, even though the phosphate trianion should be a poor leaving group. However, nucleophilic attack upon a phenyl group is generally insensitive to the nature of the leaving group[25] suggesting the reaction below.



The 2,4- and 2,6-dinitrophenyl phosphates differ considerably in their reactions with methoxide ion, because with the 2,6 compound ether is the major product, suggesting that the second nitro group assists nucleophilic attack upon the phenyl group, as is found in other aromatic nucleophilic substitutions. The electronic effect of the nitro groups should be greatest when they are in the *ortho* positions. So far as attack upon phosphorus is concerned electronic effects should be less, and steric effects more, important. There is much more phosphorus–oxygen fission in the alkaline methanolysis of the 2,4- than the 2,6-dinitrophenyl phosphate (Tables XII and XIII).

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# The Temperature Dependence of the Hydrolysis of a Series of Substituted Benzylidene-1,1-dimethylethylamines[1]

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*Contribution No. 1423 from the Department of Chemistry, Indiana University, Bloomington, Indiana.* *Received July 18, 1966*

**Abstract:** Activation parameters have been determined for the hydrolysis of a series of benzylidene-1,1-dimethylethylamines in aqueous solutions under conditions of pH in which (a) attack of hydroxide ion on the protonated substrates is rate determining, (b) attack of water on the protonated substrates is rate determining, and (c) decomposition of the carbinolamine intermediates is rate determining. In basic solution, condition a above, enthalpies and entropies of activation, calculated from first-order, pH-independent rate constants, vary in a random fashion as the nature of the polar substituent in the benzaldehyde moiety is varied, although the free energies of activation are nearly independent of this parameter. At slightly acidic values of pH, condition b above, values of $\Delta H^{\ddagger}$ near 13 kcal/mole and of $\Delta S^{\ddagger}$ near $-30$ eu were obtained. These values may vary somewhat with the nature of the polar substituent although definite trends have not been established. In 0.1 $M$ HCl, condition c above, values of $\Delta H^{\ddagger}$ increase regularly with increasing electron-donating power of the polar substituent; those for $\Delta S^{\ddagger}$ are independent of the nature of the polar substituent.

The kinetics of hydrolysis of Schiff bases derived from both aromatic and aliphatic amines has received considerable attention during the last few years.[3–13] Conclusions regarding reaction pathways and transition state structures drawn from these studies have been corroborated and complemented by investigation of the reverse reaction, the addition of nitrogen nucleophilic reagents to carbonyl compounds.[3,5,12,14–16] As a result, certain aspects of these reactions, including the effect of structure on reactivity and the effect of pH on rate, seem to be clearly understood. Other aspects, such as the precise transition-state structure for those reactions involving general acid–base catalysis, are less clearly resolved.[9,12,14,17–19] One noticeable gap in information regarding these reactions, and one that might on closing shed light on unresolved issues, is the lack of activation parameters for the various steps in the reaction sequence. In the few cases in which activation parameters have been measured, it is frequently unclear which step in the over-all process is rate determining under the reaction conditions employed. This manuscript reports a study of the temperature depen-

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(2) Career Development Awardee of the National Institute of Health.

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