Solvolysis of α-Arylvinyl Ethyl Phosphates in Aqueous and Methanolic Solutions: Intramolecular Participation by the [(Ethyloxy)phosphoryl]oxy Group

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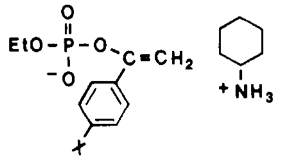
The α-arylvinyl ethyl phosphates **2a–c** were synthesized and their solvolysis reactions were studied in acidic aqueous solution and methanol. In aqueous solution both the anionic and neutral diesters are subject to acid-catalyzed hydrolysis. Solvent deuterium isotope effects, the observation of general acid catalysis by formic acid, and comparisons with the reaction characteristics of the acid-catalyzed hydrolysis of other vinyl esters and ethers indicate that the anionic diesters hydrolyze via an $A_{SE}2$ mechanism. The ratio of the rate constants for hydronium ion catalyzed hydrolysis of anionic and protonated **2c**, k_-/k_0, is 14.1 ± 0.3. This modest acceleration is consistent with weak electrostatic stabilization of the developing cation by the anionic site, although an inductive effect must also contribute. A previously reported correlation of log k_{H^+} for a series of alkenes of the type $R_1R_2C{=}CH_2$ with the sum of the $\sigma_P{}^+$ parameters for R_1 and R_2 and k_- for **2a** at 25 °C were used to calculate a value of –0.52 for the $\sigma_P{}^+$ parameter of the anionic [(ethyloxy)phosphoryl]oxy group. The estimated $\sigma_P{}^+$ of the protonated group is –0.43. These parameters and direct comparisons of hydrolysis rates of **2a–c** with the hydrolysis rates of the corresponding triesters **1a–c** and the α-arylvinyl methyl ethers confirm that the [(ethyloxy)phosphoryl]oxy group, in both of its ionization states, is intermediate between a [bis(alkyloxy)-phosphoryl]oxy group and an alkoxy group in its ability to stabilize a cation. The solvolysis of **2a–c** in methanol/HCl proceeds via two routes. An HCl-catalyzed pathway has characteristics very similar to the acid-catalyzed hydrolysis reactions. Another path, the rate of which is independent of HCl concentration, apparently involves intramolecular general acid catalysis of methanolysis by the protonated [(ethyloxy)phosphoryl]oxy group. Differences in the ionization constants of the diesters in the two solvents apparently account for the divergent solvolysis behavior.

Vinyl phosphates, particularly phosphoenolpyruvate (PEP), are intermediates in a variety of biological transformations, including phosphoryl group transfer reactions[1] and the transfer of the enolpyruvyl group to nucleophilic acceptors.[2,3] Vinyl phosphate triesters possess antihelmintic and insecticidal activity associated with inhibition of acetylcholinesterase.[4]

There have been a number of investigations of the chemistry of these species.[5-10] Vinyl phosphate triesters undergo acid-catalyzed hydrolysis via an $A_{SE}2$ mechanism with C–O bond cleavage.[6,7] PEP is hydrolyzed via the expulsion of metaphosphate with no apparent participation by the carboxyl group.[8] Triester and diester derivatives of PEP undergo hydrolysis via intramolecular nucleophilic attack of the carboxyl group with P–O bond cleavage.[9,10]

With the exception of monobenzyl phosphoenolpyruvate, the chemistry of which is dominated by the carboxyl group,[10] vinyl phosphate diester chemistry has not been investigated in detail. The present study was undertaken to ascertain the role, if any, of the intramolecular [(ethyloxy)phosphoryl]oxy group, or its conjugate base, in the solvolysis reactions of vinyl phosphate diesters. The characteristics of the hydrolysis reactions of the diesters **2a–c**, formed by the monodealkylation[11] of the corresponding triesters **1a–c**, are consistent with an $A_{SE}2$ mechanism for both the neutral and anionic forms of the esters with weak electrostatic participation by the anionic phosphoryloxy group. However, in methanol **2a–c** undergo solvolysis via apparent intramolecular general acid catalysis involving the phosphoryloxy moiety.



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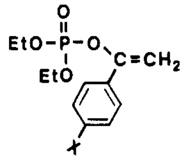

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	X
a	p-Me
b	H
c	p-NO$_2$

Experimental Section

Synthesis and Characterization of 2a–c. The diesters **2a–c** were isolated in moderate yields as the cyclohexylammonium salts after monodealkylation of the corresponding triesters, **1a–c**, with trimethylamine.[11] The triesters were prepared by reaction of the appropriate phenacyl chloride with triethyl phosphite.[5,12] Reported melting points are uncorrected. Me_4Si was used as an

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internal standard for all NMR spectra. Physical and spectral data for **2a–c** follow.

Cyclohexylammonium α-phenylvinyl ethyl phosphate (2b): mp 113–114 °C; IR(KBr) 3440, 2940, 2860, 1628, 1228, 1084, 1054 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 1.22 (3 H, t, $J_{HH} = 7.0$ Hz) 1.00–2.80 (11 H, m), 3.96 (2 H, m, $J_{HH} \simeq J_{PH} \simeq 7.0$ Hz), 5.12 (1 H, m), 5.16 (1 H, m), 7.31–7.64 (5 H, m). Anal. Calcd for $C_{16}H_{26}NO_4P$: C, 58.70; H, 8.00; N, 4.28. Found: C, 58.49; H, 8.32; N, 4.56.

Cyclohexylammonium α-(*p*-tolyl)vinyl ethyl phosphate (2a): mp 138.5–139 °C; IR (KBr) 3455, 2940, 2855, 1665, 1225, 1075, 1045 cm^{-1}; ^{1}H NMR (250 MHz, CD_2Cl_2) δ 1.21 (3 H, t, $J_{HH} = 7.0$ Hz), 1.00–2.80 (11 H, m) 2.33 (3 H, s), 3.94 (2 H, m, $J_{HH} \simeq J_{PH} \simeq 7.0$ Hz), 5.06 (1 H, m), 5.09 (1 H, m), 7.14 (2 H, d, $J = 8.2$ Hz), 7.50 (2 H, d, $J = 8.2$ Hz). Anal. Calcd for $C_{17}H_{28}NO_4P$: C, 59.81; H, 8.27; N, 4.10. Found: C, 58.45; H, 8.19; N, 4.39.

Cyclohexylammonium α-(*p*-nitrophenyl)vinyl ethyl phosphate (2c): mp 176–177 °C; IR(KBr) 3450, 3045, 2935, 2865, 1630, 1595, 1515, 1346, 1236, 1087, 1013 cm^{-1}; ^{1}H NMR (250 MHz, Me_2SO-d_6) & 1.10 (3 H, t, $J_{HH} = 7.1$ Hz) 1.00–2.80 (11 H, m), 3.76 (2 H, m, $J_{HH} \simeq J_{HP} \simeq 7.0$ Hz), 5.26 (1 H, m), 5.33 (1 H, m), 7.86 (2 H, d, $J = 8.8$ Hz), 8.20 (2 H, d, $J = 8.8$ Hz). Anal. Calcd for $C_{16}H_{25}N_2O_6P$: C, 51.61; H, 6.77; N, 7.52. Found: C, 51.64; H, 6.81; N, 7.37.

Synthesis of the Dimethyl Ketals 3a and 3b. Acetophenone Dimethyl Ketal (3b). The ketal was obtained as a colorless oil from acetophenone and trimethyl orthoformate:[13] ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.51 (3 H, s), 3.15 (6 H, s), 7.2–7.6 (5 H, m).

***p*-Methylacetophenone Dimethyl Ketal (3a).** The procedure used was identical with that used to prepare **3b**.[13] The ketal was obtained as a colorless oil: ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.50 (3 H, s), 2.30 (3 H, s), 3.14 (6 H, s), 7.0–7.5 (4 H, A_2B_2 pattern, $J = 8.4$ Hz).

Kinetic Measurements in Aqueous Solution. All water used in the kinetic measurements was distilled, deionized, and distilled again in an all glass apparatus. All kinetics, except those done at HCl concentrations above 1.0 M, were performed in solutions maintained at 1.0 M ionic strength with KCl. All HCl solutions were prepared by appropriate dilution of standardized ca. 1.0 M or 5.0 M HCl. Formic acid buffers were made from standardized ca. 1.0 M formic acid and KOH solutions and KCl. Serial dilutions were prepared from 0.5 M buffer solutions and 1.0 M KCl. DCl solutions in D_2O were prepared from standardized ca. 1.6 M DCl. Ionic strength was again maintained at 1.0 M with KCl.

pH meter readings (Orion Model 801 digital pH meter, Radiometer GK2402 combination electrode), at 50.0 ± 1.0 °C of standardized HCl solutions at 1.0 M ionic strength established that in the concentration range from 0.10 M to 0.001 M in HCl there was a constant difference between pH and the pH meter reading:

$$\text{pH} = \text{pH meter reading} - 0.07 \qquad (1)$$

This correction was applied to all measured pH values in the aqueous solutions. Measured pH values for serial dilutions of the formic acid buffers were invariant within ±0.02 pH unit.

Measurements on standardized DCl solutions at 50.0 ± 1.0 °C established a relationship between pD and the pH meter reading:

$$\text{pD} = \text{pH meter reading} + 0.27 \qquad (2)$$

This correction was applied to all pD measurments made in D_2O.

Kinetic data were gathered by monitoring changes in UV absorbance of solutions containing the phosphate esters. A Cary Model 210 UV-visible spectrophotometer equipped with thermostatted cell holders was used to record absorbance changes. The temperature used in these studies was 50.5 ± 0.1 °C.

Kinetic runs were initiated by injection of 30 μL of a ca. 0.01 M solution of the appropriate phosphate ester in ethanol into 3.0 mL of the kinetic solution which had been incubating in a cuvette in the cell holder for at least 20 min. Isosbestic points, which held for at least four half-lives, were observed at 252 nm for **2a**, 248.5 nm and 274 nm for **2b**, and 239 nm and 286 nm for **2c**. Absorption spectra recorded at the end of the reactions were identical with those of the corresponding acetophenones recorded under the same conditions. For the purposes of calculating pseudo-first-order rate constants, absorbance changes were monitored at 265 nm for **2a**, 216 nm or 266 nm for **2b**, and 266 nm for **2c**.

Pseudo-first-order rate constants were calculated from a nonlinear least-squares program developed after a method by Wentworth.[14] In all cases good agreement was obtained between observed and calculated values of A_0 and A_∞. At least two half-lives (usually 3–4 half-lives) of data were used in all the calculations.

The kinetics of hydrolysis of the triesters **1a** and **1b** were investigated over limited concentration ranges in HCl solution. Techniques employed were similar to those described above for **2a–c**.

p*Ka* Determinations. The ionization constants for **2b** and **2c** were determined at 10 ± 1 °C by titration of 0.01 M or 0.02 M solutions of **2b** or **2c** with 1.0 M HCl in a jacketed vessel to maintain temperature control. Ionic strength was maintained at 1.0 M with KCl. The titrations could not be done at higher temperatures due to the large hydrolysis rates of these compounds.

Kinetic Measurements in Methanol. Methanol used in the kinetic measurements was reagent grade solvent which was distilled at a high reflux ratio through a 150-cm column packed with glass helices. The first and last 10% of distillate were discarded. The methanol was stored at 5 °C in all glass containers protected from atmospheric moisture with paraffin seals. A stock solution of HCl in methanol was prepared by bubbling dry HCl gas (A.I.M. Products) into methanol kept at 0–5 °C in a three-necked round-bottom flask. The solution was protected from atmospheric moisture by a positive pressure of dry N_2 during this procedure. The stock solution (ca. 3.0–5.0 M) was diluted to ca. 1.0 M with dry methanol, and titrated with standardized ca. 1.0 M KOH to a phenolphthalein endpoint after an aliquot was diluted with two volumes of distilled deionized H_2O. Solutions for kinetics were prepared in the concentration range from 2.0×10^{-1} M to 5.0×10^{-4} M in HCl by dilution of the standardized ca. 1.0 M solution with dry methanol.

Solutions were also prepared from methanol-d_1, (99+% D, Merck) and DCl gas (Stohler) in the same manner as described above.

Kinetic experiments were performed as described above for the aqueous solutions.

Repetitive wavelength scans of the methanolysis reactions of **2a** and **2b** at HCl concentrations below 5.0×10^{-3} M were biphasic in nature. The initial methanolysis of the esters was followed by a second reaction that was identified as the hydrolysis of a fraction of the dimethyl ketals **3a** and **3b** by small amounts of H_2O present in the methanol. At HCl concentrations above 5.0×10^{-3} M the hydrolysis reaction was sufficiently rapid that the repetitive wavelength scans took on a typical first-order appearance.

Rate constants were calculated for the methanolysis of **2a** and **2b** by measurement of absorbance changes at isosbestic points for the subsequent hydrolysis reactions which occurred at 224.0 nm for **3a** and 216.6 nm for **3b**. This data showed clean first-order behavior for at least three to four half-lives. Absorbance vs. time data at 251 nm for **2a** and at 240 nm for **2b** were fit to a rate equation for consecutive first-order reactions (eq 7) by an iterative least-squares procedure.

The methanolysis reactions of **2c** showed first-order repetitive wavelength scans at all the HCl concentrations employed. The methanolysis reactions of **2c** were followed at 295 nm, the λ_{max} for **2c** in methanol. Isosbestic points were observed at 238 nm and 276 nm. Absorbance data collected at 295 nm exhibited clean first-order behavior for at least four half-lives.

The methanolysis of the triester **1a** was also studied. Although this ester yields a mixture of ketal **3a** and *p*-methylacetophenone under the kinetic conditions, the repetitive wavelength scans always showed clean first-order behavior with invariant isosbestic points. The hydrolysis reaction of **3a** is several orders of magnitude more rapid than the methanolysis reaction of **1a** at all HCl concentrations examined. For this reason methanolysis rate constants for **1a** were evaluated from data taken as 251 nm. This

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Table III. Least-Squares Parameters for Hydrolysis of 2a–c and 1a,b in H_2O at 50.5 °C[a]

ester	k_0,[b] M^{-1} s^{-1}	k_-,[b] M^{-1} s^{-1}	$pK_{a_{SH}}$[b]	$k_{-(AH)}$,[c] M^{-1} s^{-1}
2a		1.96 ± 0.04	0.72 ± 0.09	5.76 ± 0.56 × 10^{-3}
2b		0.55 ± 0.01	0.42 ± 0.0 (1.0 ± 0.2)[d]	1.54 ± 0.07 × 10^{-3}
2c		7.55 ± 0.40 × 10^{-3}	0.25 ± 0.01 (0.8 ± 0.2)[d]	
2c[e]	5.36 ± 0.10 × 10^{-4}	7.55 ± 0.04 × 10^{-3}	0.30 ± 0.01	1.13 ± 0.04 × 10^{-5}
1a[f]	1.86 ± 0.02 × 10^{-3}			
1b[g]	3.79 ± 0.05 × 10^{-4}			

[a] All parameters are reported with their standard deviations. [b] Determined by a fit to eq 3 or 4. [c] Determined by a fit to eq 5. [d] Determined by titration at 10 °C. [e] The values of k_0, k_-, and $pK_{a_{SH}}$ were determined by a fit to eq 4. [f] Determined from a linear least-squares fit of the log k_{obsd} vs. pH data at $[H^+] \leq 1.0$ M. [g] Average of two runs at pH 1.00 and 0.02.

absorbance data exhibited first-order behavior for at least three to four half-lives.

Isolation of *p*-Nitroacetophenone Dimethyl Ketal (3c). The diester **2c** (1.0×10^{-3} M) was solvolyzed at 50.5 °C in 0.05 M HCl in methanol for 10 half-lives as calculated from the kinetic data. At this time solid K_2CO_3 was added to neutralize the HCl and the solvent was removed by rotary evaporation. The residue was washed twice with CH_2Cl_2. The washings were combined and concentrated by evaporation. The material was then subjected to preparative-layer chromatography on silica gel (Merck, GF-254, CCl_4:CH_2Cl_2, 3:1). The only observable bands were the ketal and a small amount of *p*-nitroacetophenone. The ketal, obtained in 67% yield, had physical and spectral properties consistent with those previously reported:[13,15] mp 59–60 °C (lit.[13] mp 60–61.5 °C); ^1H NMR (60 MHz, $CDCl_3$) δ 1.53 (3 H, s), 3.18 (6 H, s), 7.67 (2 H, d, J = 8.4 Hz), 8.17 (2 H, d, J = 8.4 Hz).

Results and Discussion

Hydrolysis Reactions of 2a–c. The pseudo-first-order rate constants for the hydrolysis of **2a–c** and **1a** and **1b** at 50.5 ± 0.1 °C in HCl solutions and in formic acid buffers are reported in Tables I and II in the microfilm edition (see supplementary material). Rate constants for **1a** and **1b** are similar in magnitude to those reported previously.[6a,7] Hydrolysis rate constants for **2a–c** are dependent on both a_H, the hydrogen ion activity, and $[AH_t]$, the concentration of formic acid. Plots of log k_{obsd} vs. pH (Figure 1) deviate significantly from linearity at low pH. The rate constants for hydrolysis of **2a–c** in 1.0 M to 1.00 mM HCl solutions and the intercepts of formic acid buffer plots were fit[16] to eq 3, in which $K_{a_{SH}}$ is the ionization constant for the diester

$$k_{obsd} = \frac{K_{a_{SH}} k_- a_H}{K_{a_{SH}} + a_H} \qquad (3)$$

and k_- is as the rate constant for H_3O^+-catalyzed hydrolysis of the anionic diester. Figure 1 shows that the rate data for **2a** and **2b** are fit well by this equation. Alternative interpretations of the pH dependence of the rate constants are discussed below. The calculated values of $pK_{a_{SH}}$ and k_- are presented in Table III. The pK_a values determined by the least-squares fit are in reasonable agreement with those determined for **2b** and **2c** by titration at 10 °C (Table III).

Hydrolysis rate constants were determined for **2c** and **1a** in concentrated HCl solutions ranging from 1.5 M to 3.5 M. The results are presented in Table IV. A plot of log k_{obsd} vs. pH ($[H^+] \leq 1.0$ M) or –log $[H^+]$ ($[H^+] > 1.0$ M) for **1a** (Figure 2) shows that the hydrolysis rate constants for this ester vary linearly with pH in the dilute acid region (slope = –1.004 ± 0.003, r = 0.99996), but sharply deviate from linearity when plotted vs. –log $[H^+]$ in concentrated acid solutions.

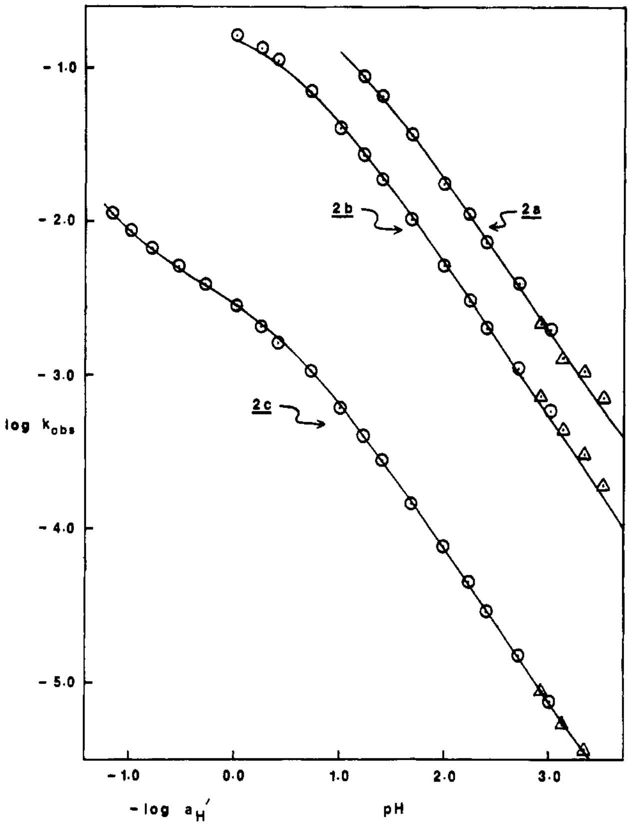

Figure 1. Plots of log k_{obsd} vs. pH ($[H^+] \leq 1.0$ M) or –log a_H' ($[H_+] > 1.0$ M, see text) for the hydrolysis of **2a–c**. Circles are data obtained from HCl solutions; triangles are the intercepts of formic acid buffer plots. Theoretical lines were obtained from fits to eq 3 for **2a,b** and eq 4 for **2c**.

Table IV. Pseudo-First-Order Rate Constants for 2c and 1a in Concentrated HCl at 50.5 °C[a]

$[H^+]$	k_{obsd} for **2c**, s^{-1} x 10^3	k_{obsd} for **1c** s^{-1} × 10^3	–log $[H^+]$	–log a_H'[b]
1.50	3.90 ± 0.02	3.59 ± 0.03	–0.18	–0.28
2.00	5.07 ± 0.03	6.44 ± 0.03	–0.30	–0.54
2.50	6.62 ± 0.03	11.52 ± 0.09	–0.40	–0.79
3.00	8.69 ± 0.03	18.58 ± 0.07	–0.48	–1.00
3.50	11.15 ± 0.04	27.9 ± 0.6	–0.54	–1.17

[a] Rate constants are reported with their standard deviations. [b] Defined in the text.

Quantitative treatment of the rate data for **2c** in concentrated acid requires an appropriate acidity function. Although the hydrolysis rates of **1b**,[7a] and other vinyl phosphate triesters[6d] have been shown to correlate with the H_0 function, it was deemed inappropriate to use this scale in the present case for two reasons. (*1*) Previously reported linear correlations of log k_{obsd} with H_0 for various vinyl phosphate triesters give slopes ranging from –0.9 to –1.4,[6d,7a] while in the present case log k_{obsd} for **1a** and **1b**

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[15] Hanzlik, R. P.; Hilbert, J. M. *J. Org. Chem.* **1978**, *43*, 610–614.

[16] A weighted non-linear least-squares procedure after the method of Wentworth (ref 14) was used in which $K_{a_{SH}}$ and k_- were varied to optimize the fit of the data.

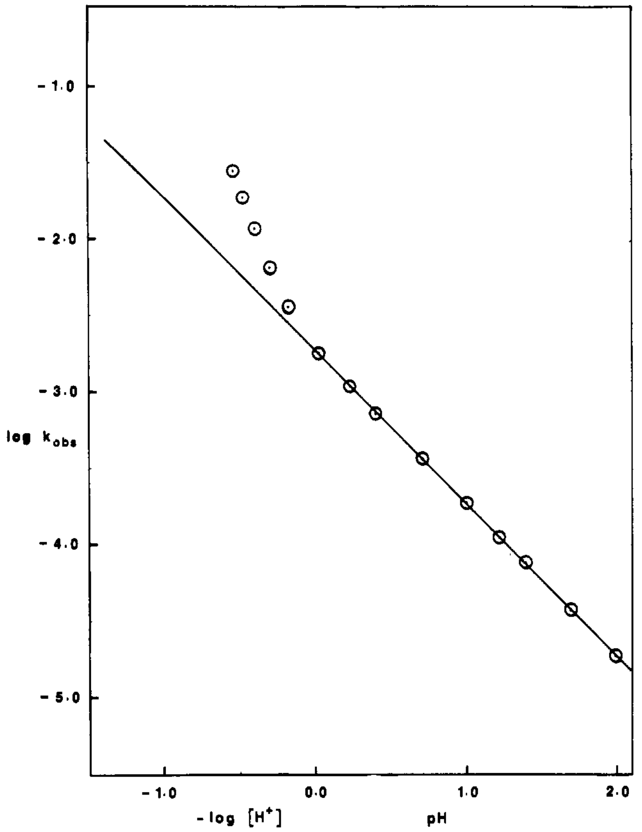

Figure 2. Plot of log k_{obsd} vs. pH ($[H^+] \leq 1.0$ M) or -log [H^+] ($[H^+] > 1.0$ M) for the hydrolysis of **1a** in HCl solutions. The theoretical line was generated from a linear least-squares fit of all data with $[H^+] \leq 1.0$ M.

correlate with pH in dilute acid with slopes of -1.0. The limiting slopes of plots of log k_{obsd} vs. pH for **2a-c** also approach a value of -1.0 in dilute acid. A plot of log k_{obsd} vs. H_0 for **2c** at $[H^+] \geq 1.0$ M shows significant upward curvature due, most likely, to the rapidly changing ratio of neutral to anionic diester in this acid concentration range. (2) In the pH region in which log k_{obsd} for the hydrolysis of **1a** is linearly dependent on pH, and the rate constants for the hydrolysis of **2a-c** are fit well by eq 3, there is considerable difference between the pH and H_0 scales.[17]

An acidity scale was constructed by adjustment of the *x* coordinate of the data points for the hydrolysis of **1a** at high acid concentration in Figure 2 until the points fell on the line extrapolated from lower acid concentrations. These adjusted *x* coordinates, $-\log a_H'$ in Table IV, were used as a measure of the "effective pH" of the concentrated acid solutions. log k_{obsd} for the hydrolysis of **1c** in concentrated acid is linearly dependent on $-\log a_H'$ with a slope of -1.07 ± 0.02 ($r = 0.9991$).[18] In addition, this acidity function provides the means for a quantitative treatment of the hydrolysis data for **2c** at high acid concentrations. The rate data for this ester can be fit[19] to eq 4, where the first term of the equation is identical with eq

$$k_{obsd} = \frac{K_{a_{SH}} k_- a_H}{K_{a_{SH}} + a_H} + \frac{k_0 a_H{}^2}{K_{a_{SH}} + a_H} \qquad (4)$$

3 and k_0 is the rate constant for H_3O^+-catalyzed hydrolysis of neutral diester. The activity of H_3O^+, a_H, is taken from pH readings at $[H^+] \leq 1.0$ M and from the acidity function based on the hydrolysis of **1a** at $[H^+] > 1.0$ M. Figure 1 shows that the rate data for **2c** are fit very well by this equation. The least-squares parameters for the fit of the hydrolysis rates of **2c** to eq 4 are also included in Table III. The values of $pK_{a_{SH}}$ and k_- are, in fact, nearly identical for the two calculations. Theoretical lines generated from the two fits differ by more than 0.01 log units only at pH values below 0.25.

The application of the acidity function derived from the hydrolysis of **1a** to eq 4 for the reactions of **2c** requires the assumption that ΔG^* for the hydrolysis of the neutral diester, and also ΔG for the ionization of **2c**, vary with acidity in a manner which is directly proportional to the change in ΔG^* for the hydrolysis of **1a** with acidity. Although these are highly restrictive assumptions, the data is fit very well by eq 4. Nevertheless, the correlation was restricted to as small an acid concentration range as was practical to obtain a value for k_0 with reasonable precision.

The hydrolysis rates of **2a-c** in formic acid buffers can be fit by eq 5, where k_I, the intercept of the buffer plots,

$$k_{obsd} = k_I + \frac{K_{a_{SH}} k_{-(AH)} f_{AH} [AH_t]}{K_{a_{SH}} + a_H} \qquad (5)$$

is H_3O^+ dependent, f_{AH} is the fraction of free formic acid in the buffer, and $k_{-(AH)}$ is the rate constant for formic acid catalyzed hydrolysis of the anionic diester. $K_{a_{SH}}$ are the values obtained from the nonlinear least-squares fit of the H_3O^+ dependent data to eq 3 (**2a,b**) or eq 4 (**2c**). No terms attributable to general base catalysis or to general acid catalyzed hydrolysis of the neutral diester were detectable. The latter would be difficult to detect at the pH values of the buffer solutions employed in the study. The values of $k_{-(AH)}$ are included in Table III.

Although the pH dependence of the second term of eq 4 most certainly indicates H_3O^+-catalyzed hydrolysis of the neutral diester, the interpretation of the first term is more ambiguous. Two kinetically indistinguishable possibilities are H_3O^+-catalyzed hydrolysis of the anionic diester via the $A_{SE}2$ hydrolysis mechanism previously observed for vinyl phosphate triesters[6,7] and vinyl ethers,[13,20] or intramolecular general acid catalysis of hydrolysis by the protonated [(ethyloxy)phosphoryl]oxy group. The available evidence favors the first interpretation.

The carboxylic acid catalyzed hydrolyses of a variety of vinyl ethers give Brønsted correlations with an average α of approximately 0.7.[20a,b] In these correlations the point for the hydronium ion shows negative deviation from the Brønsted line so that it behaves like an acid with a pK_a of approximately 0.7 to -0.2 rather than -1.74.[20b] If the rate constant for formic acid catalyzed hydrolysis of the anion of **2a**, $k_{-(AH)}$, is assumed to fall on a Brønsted line with a slope of 0.7, then k_- for **1a** falls significantly below that line. The apparent pK_a of the hydronium ion is -0.2, in good agreement with previous observations. In fact, $k_{-(AH)}$ and k_- for **2a** are very similar in magnitude to the corresponding constants for ethyl vinyl ether,[20a] although the data for **2a** were obtained at a temperature 25 °C higher.

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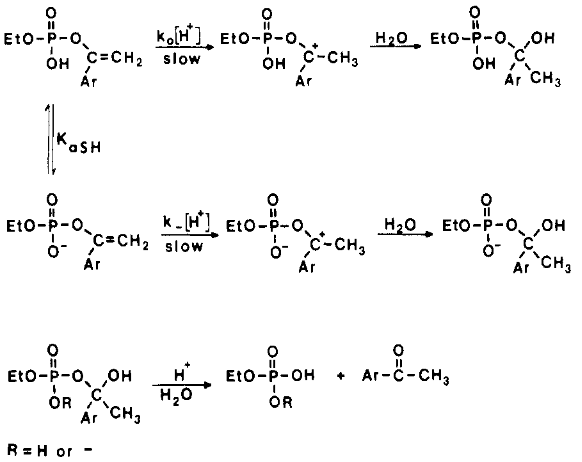
[17] Paul, M. A.; Long, F. A. *Chem. Rev.* **1957**, *57*, 1-45.

[18] Novak, M.; Roy, K. R. Unpublished results.

[19] $K_{a_{SH}}$, k_-, and k_0 were treated as variable parameters in a weighted non-linear least-squares calculation after the method of Wentworth (ref 14).

[20] (a) Kresge, A. J.; Chen, H. L.; Chiang, Y.; Murrill, E.; Payne, M. A.; Sagatys, D. S. *J. Am. Chem. Soc.* **1971**, *93*, 413-423. (b) Kresge, A. J.; Chen, H. J. *Ibid.* **1972**, *94*, 2818-2822. (c) Kresge, A. J.; Chiang, Y. *J. Chem. Soc. B* **1967**, 53-57. (d) Kresge, A. J.; Sagatys, D. S.; Chen, H. L. *J. Am. Chem. Soc.* **1977**, *99*, 7228-7233. (e) Chwang, W. K.; Eliason, R.; Kresge, A. J. *Ibid.* **1977**, *99*, 805-808. (f) Kresge, A. J.; Chiang, Y. *Ibid.* **1973**, *95*, 803-808. (g) Kresge, A. J.; Chwang, W. K. *Ibid.* **1978**, *100*, 1249-1253.

Scheme I



The ratio of the rate constants for H_3O^+-catalyzed hydrolysis of the anionic and neutral diester of **2c**, k_-/k_0, is 14.1 ± 0.3. Similar ratios are observed for the hydrolysis of vinyl ethers containing intramolecular carboxyl groups.[13,21] The accelerations caused by the carboxylate anion in these hydrolysis reactions are apparently due to a combination of inductive and resonance effects, and weak electrostatic stabilization of the developing cation by the anionic site.[13,21] Electrostatic effects have also been observed in the intramolecular general acid catalyzed hydrolysis of vinyl ethers.[20e,f] Negatively charged acids are ca. 5–10 times more efficient catalysts of hydrolysis of vinyl ethers than are uncharged acids of similar statistically corrected pK_a.[20e] Resonance effects are not possible in the present case. The observed acceleration is probably caused primarily by an electrostatic effect,[22] but an inductive effect must also contribute.

Other characteristics of the hydrolysis reactions of **2a–c** are fully consistent with an $A_{SE}2$ mechanism. Solvent deuterium isotope effects measured for the hydrolysis of **2b** in the pH range 1.0–3.0 are apparently invariant to pH with an average value $k_{H_3O^+}/k_{D_3O^+}$ of 2.66 ± 0.14. This is consistent with the hydrolysis reactions of other vinyl esters and ethers which show a solvent deuterium isotope effect for the H_3O^+-catalyzed reaction in the range 2.5–4.0.[7a,13,20b,d,23] These values are consistent with a mechanism involving proton transfer in the rate-determining step. The observation of general acid catalysis by formic acid is further evidence for such a process.

Correlation of the hydrolysis rate constants at 70 °C for a series of diethyl α-arylvinyl phosphates, including **1a–c**, with the σ^+ parameter for the substituent in the aryl ring gives a slope, ρ, of −2.1.[6a] A similar correlation for the hydrolysis of a series of α-arylvinyl methyl ethers gives a slope of −2.25.[13] A plot of log k_- vs. σ^+ for the more limited series of esters **2a–c** gives a slope of −2.26 ± 0.08. Similarly, the $k_{-(AH)}$ constants give a calculated slope of −2.62 ± 0.14. These values are consistent with the development of a positive charge on the α-carbon of the vinyl group in the rate-determining step.

All the available data for the hydrolysis of **2a–c** in aqueous acid is consistent with the $A_{SE}2$ mechanism of Scheme I in which both the neutral and anionic diester are subject to hydrolysis. Nucleophilic attack by H_2O on the cation after the rate-determining step would lead to the observed acetophenone products via a mechanism involving C–O bond cleavage which has been shown to be the case for the acid-catalyzed hydrolysis of **1b**.[6b,c] It is likely that the hydration of the cationic intermediate is general base catalyzed.[20g]

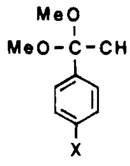
It has been shown previously that the H_3O^+-catalyzed hydrolysis rate constants at 25 °C of a large series of alkenes of the type $R_1R_2C{=}CH_2$ are well correlated with the sum of the σ_P^+ parameters for R_1 and R_2 by eq 6.[24] The

$$\log k_2 = -12.3\sum\sigma_P^+ - 10.1 \tag{6}$$

σ_P^+ of the [bis(ethyloxy)phosphoryl]oxy group (−0.13), obtained from the rate of hydrolysis of a suitably substituted cumyl chloride derivative, was used to show that the correlation was valid for a series of vinyl phosphate triesters also.[6d]

The σ_P^+ parameter for the anionic [ethyloxy)-phosphoryl]oxy group can be calculated from k_- for **2a** at 25 °C (1.9×10^{-1} M^{-1} s^{-1})[25] and σ_P^+ for the p-tolyl group (−0.24),[26] provided that eq 6 remains valid. The value obtained is −0.52. The σ_P^+ parameter for the protonated [ethyloxy)phosphoryl]oxy group can be estimated to be −0.43 if the ratio k_-/k_0 for **2a** is the same as for **2c**. These values are intermediate between those for OH (−0.92) and OCH_3 (−0.78)[27] and the σ_P^+ parameter for [bis(ethyloxy)phosphoryl]oxy (−0.13). Direct comparison of hydrolysis rate constants for **2a–c** with those for **1a–c**[6a,7] and the corresponding methyl vinyl ethers[13] leads to the same conclusion: the cation stabilizing ability of the [(ethyloxy)phosphoryl]oxy group, in both of its ionization states, is intermediate between that for the [bis(ethyloxy)-phosphoryl]oxy group and an alkoxy or hydroxy group.

Solvolysis of 2a–c in Methanol. The kinetics of the solvolysis of **2a** and **2b** in methanol were complicated by the observation of non-first-order behavior under certain conditions. At low HCl concentrations (<5 × 10^{-3} M) the solvolysis of these esters occurred in two consecutive steps. The methanolysis of the esters was followed by the hydrolysis of a portion of the dimethyl ketal products **3a** and **3b** by residual H_2O remaining in the methanol. Isosbestic points for the hydrolysis in this solvent of the authentic ketals, 224.0 nm for **3a** and 216.6 nm for **3b**, were in agreement with those obtained for the second of the two processes undergone by the esters. Infinity absorbance spectra obtained from the methanolysis of **2a** and **2b** were essentially identical with those obtained at the completion of the hydrolysis reactions of **3a** and **3b**. Absorbance vs. time data for the solvolysis of **2a** and **2b** at the λ max of the two esters, 251 nm and 240 nm, respectively, were fit well[28] by eq 7 where A_∞ is the absorbance at infinite time,



3

$$A_t = A_\infty + A_1e^{-k_1t} + A_2e^{-k_2t} \tag{7}$$

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[21] Loudon, G. M.; Ryono, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 1900–1907.

[22] Wilcox, C. F.; Leung, C. *J. Am. Chem. Soc.* **1968**, *90*, 336–341.

[23] Noyce, D. S.; Pollack, R. M. *J. Am. Chem. Soc.* **1969**, *91*, 119–124.

[24] Oyama, K.; Tidwell, T. T. *J. Am. Chem. Soc.* **1976**, *98*, 947–951.

[25] Activation parameters determined over the temperature range of 20–50 °C for the k_- term of **2a** are 16.3 ± 0.2 kcal/mol (ΔH^*) and −7.1 ± 0.7 eu (ΔS^*). Novak, M.; Roy, K. R. Unpublished results.

[26] Chwang, W. K.; Knittel, P.; Koshy, K. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1977**, *99*, 3395–3401.

[27] Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* **1957**, *80*, 4979–4987.

[28] A_∞, A_1, A_2, k_1, and k_2 were all used as variable parameters in a non-linear least-squares fit of the data to eq 7 by the method of Wentworth (ref 14).

Table VI. Rate Constants, k_c and k_{HCl}, and Exponents, x, for the Methanolysis of 2a–c and 1a at 50.5 °C[a]

ester	k_c, s^{-1}	k_{HCl}, M^{-1} s^{-1}	x
2a[b]	7.22 ± 0.17 × 10^{-3}	1.10 ± 0.06 × 10^{-1}	0.94 ± 0.03
2b[b]	2.80 ± 0.03 × 10^{-3}	3.19 ± 0.14 × 10^{-2}	1.02 ± 0.03
2b in MeOD[b]	5.54 ± 0.05 × 10^{-4}	1.08 ± 0.03 × 10^{-2}	1.03 ± 0.02
2c[b]	5.48 ± 0.07 × 10^{-5}	4.18 ± 0.50 × 10^{-4}	1.04 ± 0.06
1a[c]	0.0[d]	9.64 ± 0.35 × 10^{-3}	1.10 ± 0.01

[a] Rate constants and exponents reported with their standard deviations. [b] Determined from a weighted non-linear least-squares fit to eq 8. [c] Determined from a non-weighted linear least-squares fit to log k_{obsd} = log k_{HCl} − x log [HCl]. [d] No evidence for uncatalyzed hydrolysis of **1c** was obtained at even 5 × 10^{-4} M HCl.

k_1 and k_2 are pseudo-first-order rate constants, and A_1 and A_2 are arbitrary amplitude factors. This equation has been used previously to fit absorbance data for pseudo-first-order processes involving three species.[13,29] The magnitudes of k_1 and k_2 were in excellent agreement with the rate constants for the hydrolysis of the authentic ketals and for the methanolysis of **2a** and **2b** determined from data taken at the isosbestic points of the hydrolysis reactions. For example, at 5 × 10^{-4} M HCl a fit of absorbance data at 240 nm for **2b** gave rate constants of 3.01 ± 0.05 × 10^{-3} s^{-1} and 1.22 ± 0.02 × 10^{-3} s^{-1}. The hydrolysis rate constant obtained for **3b** under the same conditions was 1.20 ± 0.03 × 10^{-3} s^{-1}, while the methanolysis rate constant for **2b**, obtained from data taken at 216.6 nm, was 2.77 ± 0.03 × 10^{-3} s^{-1}.

Infinity absorbance measurements showed that the products obtained from **2a** consisted of 35–70% *p*-methylacetophenone and those from **2b** consisted of 20–45% acetophenone.[30] The corresponding ketals **3a** and **3b** apparently made up the rest of the products since addition of H_2O to these solutions inevitably led to an increase in absorbance due to the acetophenones.

Pseudo-first-order rate constants reported in Table V in the microfilm edition (see supplementary material) for the methanolysis of **2a** and **2b** were obtained from absorbance data taken at the isosbestic points for the subsequent hydrolysis reactions. Rate constants for the solvolysis of **2b** in methanol-d_1 are also reported in Table V.

Experiments with authentic **3c** showed that it was stable under the reaction conditions, and the methanolysis of **2c** showed clean first-order behavior at all HCl concentrations studied. Infinity absorbance spectra for the methanolysis of **2c** were identical with those for **3c**, and **3c** could be isolated from the methanolysis reaction of **2c**. Pseudo-first-order rate constants for the methanolysis of **2c** are given in Table V. Methanolysis rate constants for **1a** are also reported in Table V.

A plot of log k_{obsd} vs. −log [HCl] for **1a** is linear (r = 0.99991) with a slope of −1.10 ± 0.01. However, plots of log k_{obsd} vs. −log [HCl] for **2a–c** (Figure 3) exhibit nonlinear behavior. The rate data for these esters were fit[31] by eq 8, where k_c is the rate constant for the apparently

$$k_{obsd} = k_c + k_{HCl}[HCl]^x \qquad (8)$$

uncatalyzed methanolysis of **2a–c**, and k_{HCl} is the rate constant for HCl-catalyzed methanolysis. Figure 3 shows that the methanolysis rate data for **2a–c** are fit well by eq 8. The calculated rate parameters for **2a–c** and **1a** are summarized in Table VI.

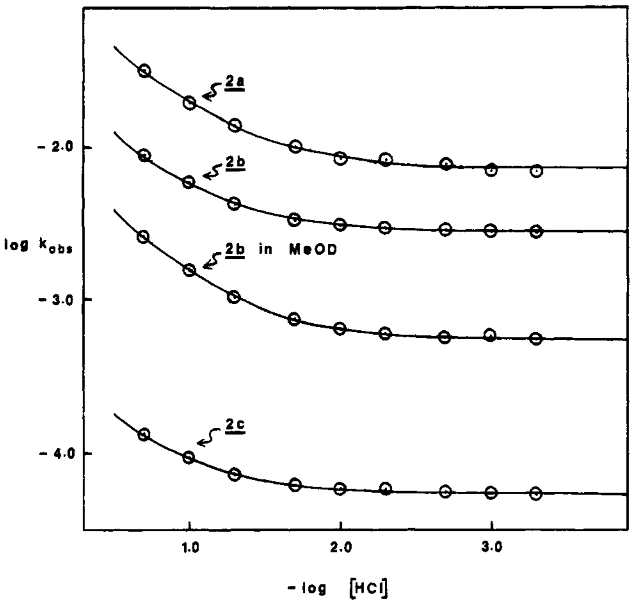

Figure 3. Plots of log k_{obsd} vs. −log [HCl] or −log [DCl] for the solvolysis of **2a–c** in methanol or methanol-d_1. Theoretical lines were generated from fits to eq 8.

The acid-catalyzed methanolysis of **2a–c** is very similar to the acid-catalyzed hydrolysis reactions of the same esters. The solvent deuterium isotope effect k_{HCl}/k_{DCl} is 2.95 ± 0.15, indicating that proton transfer occurs in the rate-determining step. A plot of log k_{HCl} vs. σ^+ for the substituent in the aromatic ring gives a slope, ρ, of −2.14 ± 0.25 which is very similar to that observed for the k_- and $k_{-(AH)}$ terms for the hydrolysis of **2a–c**, and for the acid-catalyzed hydrolysis of α-arylvinyl phosphate triesters[6a] and α-arylvinyl methyl ethers.[13]

The ionization constants for **2a–c** in methanol were not measured, however the pK_a values of didecyl phosphate and didodecyl phosphate in methanol have been reported to be 5.7 and 6.1, respectively.[32] Since the aqueous solution pK_a values of a series of dialkyl phosphates fall in the range of 1.3–1.7,[33] it appears that ΔpK_a (H_2O → MeOH) for phosphate diesters is approximately 4–5 pK units. This is consistent with the observation that ΔpK_a for carboxylic acids is ca. 5.0.[34] The pK_a values for **2a–c** in methanol, then, will fall in the range ca. 4.5–5.5, so that under the conditions of these experiments the protonated form of the ester predominates.[35] It is likely, therefore, that the k_{HCl} term of eq 8 is the rate constant for the acid-catalyzed methanolysis of the protonated ester. A mechanism which fits all the data for this reaction is given in Scheme II.

Since uncatalyzed methanolysis of the triester **1a** is not observed, the k_c rate term of eq 8 can most reasonably be interpreted as intramolecular general acid catalysis of

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[29] Moore, J. W.; Pearson, R. G. "Kinetics and Mechanism", 3rd ed.; Wiley: New York, 1981; pp. 290–296.

[30] Since the ratio [dimethyl ketal]/[acetophenone] varies linearly with [H_2O] at low [H_2O] it is possible to determine the concentration of H_2O corresponding to a given ratio of the two products from a standard curve. The relative yields of acetophenone products in the kinetics experiments indicate [H_2O] is in the range of 2–10 mM.

[31] A weighted non-linear least-squares method after Wentworth (ref 14) was used in which k_c, k_{HCl}, and x were treated as variable parameters.

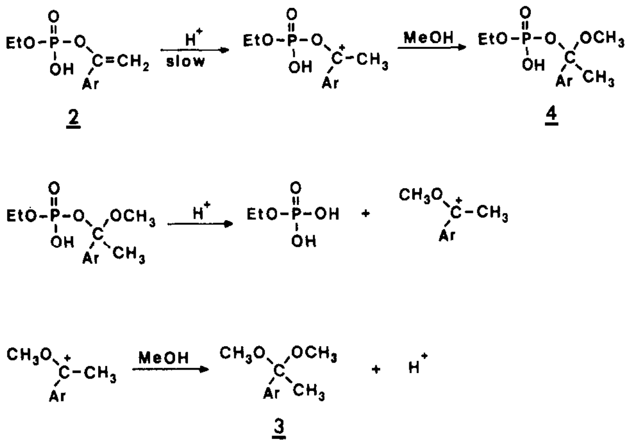
[32] Komissarenko, V. P.; Molot, L. A.; Yarnykh, A. G.; Titarenko, Yu. G. *Zh. Anal. Khim.* **1975**, *30*, 29–32.

[33] Kumler, W. D.; Eiler, J. *J. Am. Chem. Soc.* **1943**, *65*, 2355–2361.

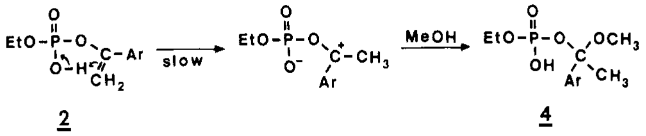
[34] Clare, B. W.; Cook, D.; Ko, E. C. F.; Mac, Y. C.; Parker, A. J. *J. Am. Chem. Soc.* **1966**, *88*, 1911–1916. Ritchie, C. D.; Uschold, R. E. *Ibid.* **1968**, *90*, 2821–2824. Ritchie, C. D.; Megerle, G. H. *Ibid.* **1967**, *89*, 1452–1453.

[35] The pK_a of HCl in pure methanol is approximately 1.1. (Kolthoff, I. M.; Chantooni, M. K. *J. Phys. Chem.* **1979**, 83, 468–474.) At the low concentrations of H_2O present in this study (ref 31) the pK_a of HCl may be somewhat lower. (Shedlovsky, T.; Kay, R. L. *J. Phys. Chem.* **1956**, *60*, 151–155. Bezman, I. I.; Verhoek, F. H. *J. Am. Chem. Soc.* **1945**, *67*, 1330–1334.)

Scheme II



Scheme III



methanolysis by the protonated [(ethyloxy)phosphoryl]oxy group, or as HCl-catalyzed methanolysis of the anion of **2a–c**. If the latter case is true, then k_c contains the ionization constant of the diester ($k_c \simeq K_{\mathrm{aSH}}k_c'$). If the ionization constant for **2c** in methanol is ca. 10^{-5} M, then the rate constant for HCl-catalyzed methanolysis of the anion, k_c', is approximately 5.0 $M^{-1}\ s^{-1}$, about 10^4 greater than the rate constant for HCl-catalyzed methanolysis of the neutral diester, k_{HCl}. The much greater effect of the anionic [(ethyloxy)phosphoryl]oxy group in methanol (k_-/k_0 in H_2O is 14.1 ± 0.3) could be attributed to the greater importance of electrostatic stabilization of the developing cation in the less polar methanol. If this is so the sensitivity of the rate of methanolysis of the anion to the substituent on the aromatic ring should be considerably less than in the methanolysis reaction of the neutral diester.[36] However, the slope of a log k_c vs. σ^+ plot is −2.06 ± 0.18, almost identical with that observed for the k_{HCl} term.[37] Since these slopes are determined from only three points their precision is low, but they do serve to indicate that there is no major difference in the sensitivity to substituent effects for the two terms of the rate law. The result is more consistent with intramolecular general acid catalysis by the phosphoryloxy group.

The solvent deuterium isotope effect, $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}}$, for the k_c term of the methanolysis of **2b**, 5.05 ± 0.07, is similar to isotope effects measured for the intermolecular general acid catalyzed hydrolysis of α-arylvinyl methyl ethers which are in the range of 5.0–7.0.[13] A mechanism for intramolecular general acid catalysis of methanolysis by the protonated [(ethyloxy)phosphoryl]oxy group is presented in Scheme III. After the intermediate 4 is produced the reaction would proceed as in Scheme II.

The results of this study indicate that in aqueous solution at moderate acidities **2a–c** undergo hydrolysis via a mechanism involving rate-limiting intermolecular protonation of the vinyl group of the anionic ester, while in methanol under similar conditions the predominant solvolysis mechanism involves rate-limiting intramolecular proton transfer from the [(ethyloxy)phosphoryl]oxy group to the vinyl group. These differences may simply be due to the differences in the acidity of the [(ethyloxy)phosphoryl]oxy group in the two solvents.

The intramolecular general acid catalysis of methanolysis is not particularly efficient compared to the HCl-catalyzed reaction. The ratio k_c/k_{HCl} for **2c** is 1.3×10^{-1} M and is somewhat lower for **2a** and **2b**. If a similar efficiency ratio applies in aqueous solution, then a rate constant of approximately $7.0 \times 10^{-5}\ s^{-1}$ can be calculated for the intramolecular general acid catalyzed pathway in water. Since this path and the hydronium ion catalyzed hydrolysis of the anion have the same pH dependence, the ratio $K_{\mathrm{aSH}}\ k_-/k_{\mathrm{c(H_2O)}}$ measures the relative rates of the two paths.[38] From the approximation made above and the kinetic parameters reported in Table III a value of approximately 50 can be calculated for this ratio for **2c**. In water the intermolecular path predominates because K_{aSH} is rather large in this solvent. However, in methanol K_{aSH} is ca. 10^{-5} M so that the intramolecular path becomes the predominant route. No doubt other factors play a role in determining the differences in solvolysis behavior of **2a–c** in the two solvents, but the differences in the ionization constants of the esters in the two solvents appears to be the dominant factor.

Registry No. **1a**, 18276-76-1; **1b**, 1021-45-0; **1c**, 34804-85-8; **2a**, 92670-54-7; **2b**, 92694-71-8; **2c**, 92670-56-9; **3a**, 53578-01-1; **3b**, 4316-35-2; **3c**, 53577-98-3; acetophenone, 98-86-2; trimethyl orthoformate, 149-73-5.

Supplementary Material Available: Tables I, II and V, pseudo-first-order rate constants for the hydrolysis and methanolysis of **2a–c** and **1a**,**b** (4 pages). Ordering information is given on any current masthead page.

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[36] Fife, T. H.; Przystas, T. J. *J. Am. Chem. Soc.* **1979**, *101*, 1202–1210.

[37] If $k_c \simeq K_{\mathrm{aSH}}k_c'$ then the slope, ρ, of a log k_c' vs. σ^+ plot would be more negative than the corresponding slope for log k_c because of the effects of the substituents on K_{aSH}.

[38] The pH dependence of the intermolecular reaction is given by eq 3, while the pH dependence of the intramolecular path is given by eq 9.

$$k_{\mathrm{obsd}} = \frac{k_{\mathrm{c(H_2O)}}a_{\mathrm{H}}}{K_{\mathrm{aSH}} + a_{\mathrm{H}}} \tag{9}$$