Reaction of Phosphonated Acetals. Acid-catalysed Hydrolysis of Dialkyl 2,2-Dialkoxyethylphosphonates

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The kinetics of the acid-catalysed hydrolysis of diethyl 2,2-diethoxyethylphosphonate (I), of diethyl 2,2-dimethoxyethylphosphonate (II), and of dimethyl 2,2-dimethoxyethylphosphonate (III) haye been studied in aqueous dioxan solution containing different acid catalysts. Plots of log k_1 against H_0 had slopes of 0.98; plots of (log k_1 + H_0) against log a_{H_2O} had slopes w = −0.1. The deuterium solvent isotope effect k_D/k_H for compound (II) in 1M-sulphuric acid at 30° was 2.8. According to the hypotheses of Zucker–Hammett and of Bunnett, the results obtained are in agreement with an A-1 mechanism. The measured second-order rate constants at 25° were: k_2 3.7 × 10^{-4} l mol s^{-1} for compound (I) and 1.7 × 10^{-4} l mol s^{-1} for compounds (II) and (III). Low values of the energy (15—17 kcal mol^{-1}) and entropy (−25 to −27 cal mol^{-1} K^{-1}) of activation were observed. The substituents at the central carbon atom show the expected polar effects, without any measurable steric effects. The observed values of the energy and entropy of activation are correlated with the polarity of the phosphoryl group. An effect of intramolecular catalytic influence is introduced. The products of hydrolysis were identified as the corresponding aldehydes; that of compounds (II) and (III) is the novel dimethyl formylmethyl phosphonate.

THE hydrolysis of acetals has been extensively studied. There is general acceptance that the reaction proceeds by an A-1 mechanism,[1] although special cases have been reported,[2] in which an A-2 reaction is predominant. The presence of the phosphoryl group, $P^+ \longrightarrow O^-$, can be anticipated to result in a polar withdrawing effect. Determination of the Taft substituent constant σ^* by measurement of the pK_a of acetic acid substituted by a diethoxyphosphono-group showed that this group has moderately electron-attracting properties (σ^* 0.78).[3] No other effects, especially steric, have been reported.

Acid-catalysed hydrolysis of open-chain acetals, $R^1R^2C(OC_2H_5)_2$, where R^1 and R^2 are non-conjugated, simple groups, showed that steric effects are of secondary importance by comparison with polar and resonance effects.[4] However, the probability was not completely excluded that the presence of bulky groups near the central carbon atom may influence the reaction pathway. Special interest in these systems is aroused by the possible participation of the phosphoryl group in the structure of the transition state. In the present work, the acid-catalysed hydrolysis of a series of dialkyl 2,2-dialkoxyethylphosphonates (I)—(III) was determined in order to elucidate the relative importance of the polar, inductive, and steric effects of the dialkoxyphosphonate group on the hydrolysis of acetals. Compound (I) has been previously reported;[5] compounds (II) and (III) were newly synthesized by an analogous procedure.

$$(R^1O)_2P(O)CH_2CH(OR^2)_2$$

$$\text{(I) } R^1 = R^2 = C_2H_5$$

$$\text{(II) } R^1 = C_2H_5,\ R^2 = CH_3$$

$$\text{(III) } R^1 = R^2 = CH_3$$

EXPERIMENTAL

N.m.r. spectra were taken on a Varian A-60 instrument for solutions in $CDCl_3$ with tetramethylsilane as internal standard.

Diethyl 2,2-*Diethoxyethylphosphonate* (I).—Compound (I) was synthesized by the Arbuzov reaction between freshly distilled chloroacetaldehyde diethyl acetal (85.5 g, 0.557 mol) and triethyl phosphite (93.6 g, 0.563 mol), as in the previously reported procedure, which however used bromoacetaldehyde diethyl acetal.[5] The course of the reaction was followed by withdrawing samples (0.05 ml each) and titration of triethyl phosphite by an iodine solution in carbon tetrachloride.[6] After 50 h <2% triethyl phosphite remained; the reaction mixture was distilled in a vacuum, b.p. 86—90 °C at 0.3 Torr, yielding a liquid (110.2 g, 78.6%), δ 1.23 [12 H, dt (as a q), J 7 Hz, 4 CH_3], 2.18 (2 H, dd, J_{P-H} 18, J_{CH_2-CH} 6 Hz, PCH_2C), 3.6 [4 H, octet(2q), J 7 Hz, $CH(OCH_2CH_3)_2$], 4.1 [4 H, 2 quintets, J 7 Hz, $P(OCH_2CH_3)_2$], and 4.9 [1 H, dt, J 6 Hz, $CCH(OEt)_2$].

Diethyl 2,2-*Dimethoxyethylphosphonate* (II).—Compound (II) (38.9%) was similarly prepared, using triethyl phosphite and chloroacetaldehyde dimethyl acetal, but with refluxing for 5 days, b.p. 93—94° at 1.5 Torr, δ 1.32 (6 H, t, J 7 Hz, 2 CH_3), 2.2 (2 H, dd, J_{P-H} 18, J_{CH_2-CH} 6 Hz, PCH_2C), 3.38 [6 H, s, $C(OCH_3)_2$], 4.17 [4 H, 2 quintets, J 7 Hz, $P(OCH_2CH_3)_2$], and 4.92 [1 H, dt, J 6 Hz, $CCH(OMe)_2$].

Dimethyl 2,2-*Dimethoxyethylphosphonate* (III).—Compound (III) (21%) was prepared, using trimethyl phosphite and chloroacetaldehyde dimethyl acetal, but with refluxing for 7 days, b.p. 73—78 °C at 2 Torr, δ 2.2 (2 H, dd, J_{P-H} 18, J_{CH_2-CH} 6 Hz, PCH_2C), 3.35 [6 H, s, $C(OCH_3)_2$], 3.78 [6 H, s, J 18 Hz, $P(OCH_3)_2$], 4.92 [1 H, dt, J 6 Hz, $CCH(OCH_3)_2$].

Diethyl Formylmethylphosphonate.—To compound (I) (45 g, 0.177 mol) was added 2.5N-HCl (5 ml) and the solution was refluxed under nitrogen for 2 h. The product (24 g, 75%) was vacuum-distilled, b.p. 85—90 °C at 0.2 Torr (lit.,[5b] 100—103 °C at 0.8 Torr), n_D^{24} 1.432 0 (lit.,[5a] n_D^{20} 1.435 5), δ 1.3 (6 H, t, J 7 Hz, $2CH_3$), 3.1 (2 H, dd, J_{P-H} 21, J_{CH_2-CH} 3.5 Hz, PCH_3C), 4.2 [4 H, d quintet, J 7 Hz, $P(OCH_2CH_3)_2$], and 9.68 (1 H, dt, J_{P-H} 3.5, J_{CH_2-CH} 1.5 Hz, CHO), 2,4-dinitrophenylhydrazone (Found: N, 15.65; P, 8.5. Calc. for $C_{12}H_{17}N_4O_7P$: N, 15.55; P, 8.6%), m.p. 108—109 °C (lit.,[5a] 111—112 °C), $\lambda_{max.}$ 298 nm (ε 85 l mol^{-1} cm^{-1}).

Dimethyl Formylmethylphosphonate.—To compound (III) (26.5 g, 0.134 mol) was added 2.5N-HCl (6 ml) and this was followed by treatment as above to give the *formyl derivative* (15 g, 73%), b.p. 68—69 °C at 0.15 Torr, n_D^{24} 1.441 5,

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δ 2.25 (2 H, dd, J_{P-H} 19, J_{CH_2-CH} 6 Hz, PCH_2C), 3.78 [6 H, d, J 12 Hz, $P(OCH_3)_2$], and 9.75 (1 H, dt, J_{P-H} 3.5, J_{CH_2-CH} 1 Hz, CHO), 2,4-*dinitrophenylhydrazone* (Found: N, 16.8; P, 9.25. $C_{10}H_{13}N_4O_7P$ requires N, 16.9; P, 9.3%), m.p. 178—179°, $\lambda_{max.}$ 265 nm (ε 65 l mol^{-1} cm^{-1}).

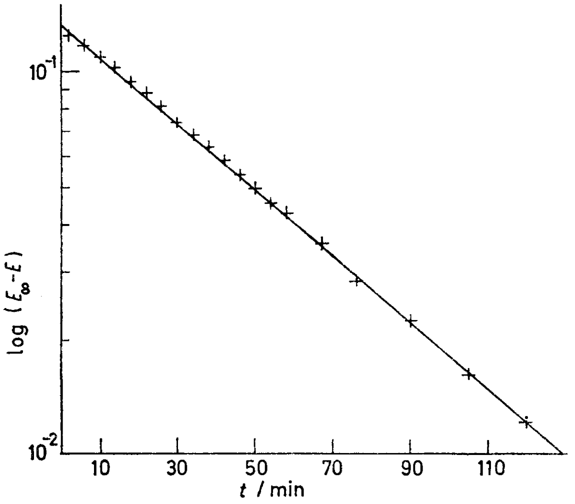

FIGURE 1 Plot of log (E_∞ − E) against time for compound (II) in aqueous 4% dioxan with 0.98M-$HClO_4$ at 35 °C

The i.r. spectra of the acetals and aldehydes synthesized show characteristic bands for P=O, P–O–alkyl, $CH(OR)_2$, and CHO vibrations identical with those given by ref. 5.

Kinetic Measurements.—Kinetic measurements were performed at several concentrations of hydrochloric and perchloric acid. Portions (2.0 ml) of a 10% (v/v) solution of the acetals in dioxan were diluted to 50.0 ml by an aqueous solution of the acid. The progress of the reaction was followed spectrophotometrically (Zeiss PM QII or Gilford 250 instruments), in 2 cm optical path quartz cells by observing the carbonyl group absorption of the aldehyde formed, either at 298 nm for compounds (I) and (II) or at 265 nm for compound (III). The temperature of the cell mounting block was thermostatted by water circulation to within ±0.1 °C. The rate constant was evaluated from the slope of log (E_∞ − E) *versus* time by the least squares method, or by the Guggenheim–Mangelsdorf method,[7] using paired values of the absorbance E separated by a constant time interval, Δt. A typical result is shown in Figure 1. Least-squares treatments were also used in order to find the energies and entropies of activation from the plot of log k *versus* $1/T$.[8]

Solvent isotope effects in the hydrolysis were measured using 1M-sulphuric acid dissolved in 99.7% D_2O (Carl Roth).

RESULTS AND DISCUSSION

To study the nature of the hydrolysis of dialkyl 2,2-dialkoxyethylphosphonates the reaction was carried out at different acid concentrations and temperatures. Table 1 presents the first-order rate constants at 25 °C. The observed data indicate good correlation with the Hammett acidity function, $-H_0$, with a slope of 0.98 ± 0.06. Accordingly, as shown in the sixth column of Table 1, log k_1 + H_0 has a constant value, within the limits of the experimental accuracy.[9] In an alternative representation of acid-catalysed hydrolysis, as proposed by Bunnett, the slopes w of plots of (log k_1 + H_0) against the logarithm of water activity are taken as a mechanistic criterion.[10] For the hydrolysis of acetals in perchloric acid typical w values were reported to be zero to −2.[10b] Plots of (log k_1 + H_0) against log a_{H_2O} are shown in Figure 2 for the three acetals examined. A straight line through these points has a slope nearly zero or slightly negative (−0.08 to −0.12).

TABLE 1

Rate constants for the hydrolysis of acetals (I)—(III) in aqueous 4% dioxan at 25° as a function of acid concentration and the Hammett acidity function H_0 [a]

Compound	Acid	Conc. (M)	10^4k_1/ s^{-1}	$-H_0$	log k_1 + H_0	10^4k_2/ l mol^{-1}s^{-1}
(I)	HCl	0.9	3.7	0.12	−3.55	
(I)	HCl	1.83	12.4	0.465	−3.37	4
(I)	HCl	2.74	20.6	0.815	−3.50	
(I)	$HClO_4$	0.98	4.8	0.155	−3.47	
(I)	$HClO_4$	1.49	9.25	0.395	−3.43	
(I)	$HClO_4$	1.98	15.6	0.635	−3.44	3.7
(I)	$HClO_4$	2.23	18.8	0.750	−3.48	
(I)	$HClO_4$	2.62	21.8	0.925	−3.59	
(II)	$HClO_4$	0.5	0.95			
(II)	$HClO_4$	0.98	1.5	0.155	−3.98	
(II)	$HClO_4$	1.49	3.5	0.395	−3.85	1.7
(II)	$HClO_4$	1.98	4.2	0.635	−4.01	
(II)	$HClO_4$	2.62	8.9	0.925	−3.97	
(III)	$HClO_4$	0.98	1.8	0.155	−3.90	
(III)	$HClO_4$	1.49	3.4	0.395	−3.86	
(III)	$HClO_4$	1.98	4.0	0.635	−4.03	
(III)	$HClO_4$	2.62	7.5	0.925	−4.04	

[a] In accordance with values determined in ref. 9.

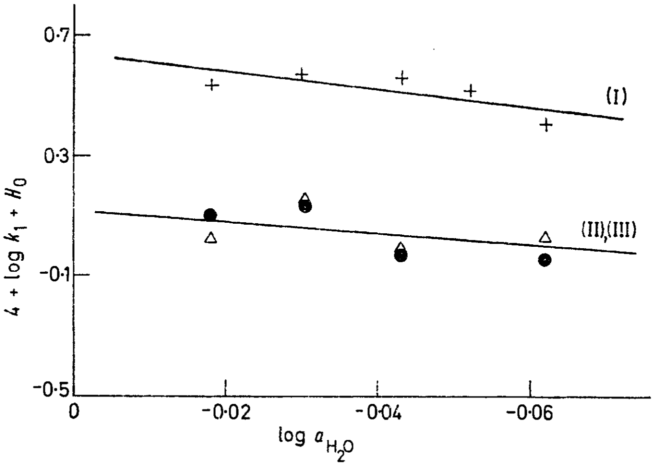

FIGURE 2 Plot of (log k_1 + H_0) against log a_{H_2O} for compounds (I) (+), (II) (△), and (III) (●) in different perchloric acid concentrations at 25 °C

The second-order rate constant for the hydrolysis of compound (II) at 30 °C is 1.99 × 10^{-4} l mol^{-1} s^{-1}. Replacing the water by an equal volume of D_2O (99.7%)

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increases the rate to 5.54×10^{-4} l mol^{-1} s^{-1}. The ratio k_D/k_H is thus 2.8, in the range normally found in *A*-1 acetal hydrolysis reactions.[11]

Extrapolation of the plot of k_1 as a function of the acid concentrations to zero acid concentration indicates that there is no significant uncatalysed reaction of the neutral molecule. All the above evidence points to an *A*-1 reaction, the first step including a fast protonation of the substrate, followed by a slow, rate-determining step, leading to the oxonium ion, and concluded by a fast reaction with water to give the products.

Kreevoy and Taft,[4] analysing the acid-catalysed hydrolysis of a series of 24 acetals, found that, when resonance effects are excluded, the log rate constants show a linear dependence on the polarity and hyperconjugation effects of the substituents [equation (1)

$$\log (k/k_0) = (\Sigma\sigma^*)\rho^* + (\Delta n)h \qquad (1)$$

where k is the second-order rate constant for the general acetal $R^1R^2C(OC_2H_5)_2$, k_0 is the rate constant for the standard of comparison, $(CH_3)_2C(OC_2H_5)_2$, $\Sigma\sigma^*$ is the sum of the σ^* values for R^1 and R^2, ρ^*, a parameter characteristic of the reaction series, is a measure of the relative susceptibility to the polar effects of substituents, (Δn) is the difference between the number, n, of α-hydrogen atoms in R^1 and R^2 and the corresponding number of α-hydrogen atoms in the standard, *i.e.* $\Delta n = n - 6$, and h is an empirical constant (0.54 ± 0.06) attributable to the stabilisation of the reaction transition state by a single α-hydrogen atom [4]]. Taking the σ^* values for the H and the $CH_2P(O)(OC_2H_5)_2$ groups as 0.49 and 0.78, respectively,[3] we obtain for compound (I) $\Sigma\sigma^* = 0.49 + 0.78 = 1.27$. Applying this $\Sigma\sigma^*$ to the linear plot of $\log (k/k_0) - (\Delta n)h$ *versus* $\Sigma\sigma^*$ (Figure 2 of ref. 4), we obtain a *predicted* value of $\log (k/k_0) - (\Delta n)h = -4.46$. From the slope of k_1 *versus* [H$^+$] for compound (I) at low acid concentration we find the second-order rate constant $k = 3.7 \times 10^{-4}$ l mol^{-1} s^{-1}, while for the reference compound, acetone diethyl acetal, $k_0 = 7.52 \times 10^{2}$ l mol^{-1} s^{-1}.[4] Since $n = 2$ and hence $\Delta n = -4$, we get $\log (3.7 \times 10^{-4}/7.52 \times 10^{2}) + 0.54 \times 4 = -4.16$. This *observed* value differs by only 0.3 log units from the above predicted value of -4.46. Such a deviation is small enough not to require any significant contribution by steric effects.

It is generally accepted that the hydrolysis of an acetal is characterized by activation energies of *ca.* 25 kcal mol^{-1}.[12] The activation energies obtained from our observed rate constants (see Figure 3) are remarkably low, in the range of *ca.* 15 kcal mol^{-1} (Table 2).

On theoretical grounds such a case has to be studied from the point of view of the transition state linked to the rate-determining step. Aksnes and Gramstad pointed out the strong polar effect of the phosphoryl group due to the p_π–d_π bonding.[13] In a phosphonate group, in which alkoxy-groups are directly linked to the phosphorus atom, there is an increase in the polarity of the P=O bond due to the mesomeric effect (+*M*). By showing that it is the phosphoryl group which participates in hydrogen bonding, Aksnes and Gramstad were able to treat these effects quantitatively from the frequency shifts for the hydrogen bond complexes between phenol and phosphoryl compounds.

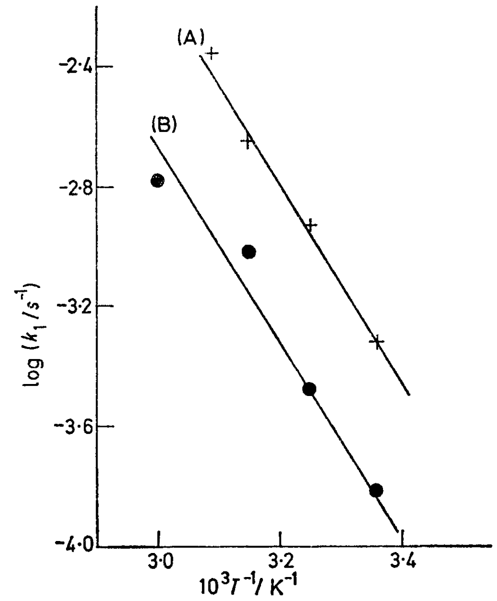

FIGURE 3 Plot of log k_1 against $1/T$ for compounds (I) (A) and (II) (B)

TABLE 2

Thermodynamic functions calculated for the hydrolysis of acetals (I) and (II) in 1M-acid

Compound	Acid	10^4k_1/s^{-1} 25°	35°	45°	50°	60°	E_a/ kcal mol^{-1}	$\Delta S^\ddagger$/ cal mol^{-1} K^{-1}
(I)	HCl	4.5	10.5		45		17	−26
(I)	HClO$_4$	4.8	11.8	22.4	43.7		14.9	−25
(II)	HClO$_4$	1.5	3.3	9.6		16.5	14.9	−27

Aksnes [14] also studied nucleophilic displacements of phosphorus compounds, deducing that the polarity and polarisability of these compounds results in significantly decreased activation energies. Although the intramolecular catalysis by a carboxy- [15] and by a hydroxy-group [16] has been realized in the hydrolysis of acetals, a possible participation of a phosphoryl group was not observed in previous studies. Figure 4 indicates the stepwise formation of intermediates, resulting in a lowering of the activation energy. The phosphoryl group is located in a position which enables hydrogen bonding with an alkoxy-group of the acetal. Due to its high polarity the phosphonate group quickly picks up a

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proton from the acidic medium, and then spreads out its charge by hydrogen bond formation. The intermediates (In1) and (In2) are stabilised by six-membered cyclic structures, analogous to a quinone ring.[16]

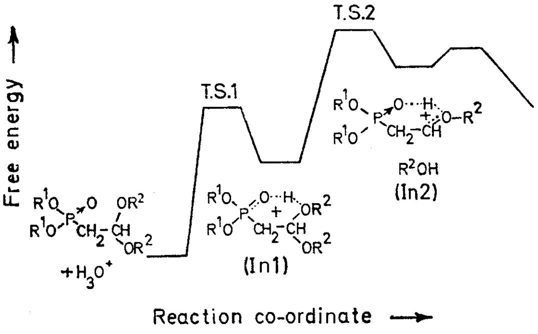

FIGURE 4 Diagram of free energy against the reaction co-ordinate for a specific-acid catalysed hydrolysis of phosphonated acetals

Use of the entropies of activation as a further mechanistic criterion seems to fail in our case. *A*-1 Reactions are presumed[17] to have entropies of activation near zero or small positive values. The values calculated for our experiments dropped to *ca.* —26 cal mol^{-1} K^{-1}, which resembles typical values for *A*-2 reactions. This ambiguity may be solved by the proposed scheme shown in Figure 4. The formation of the six-membered cyclic structures results in reduction of rotational and translational degrees of freedom.

In the hydrolysis of *o*-hydroxybenzaldehyde diethyl acetal,[16] where a similar intramolecular influence is exercised by the hydroxy-group, $\Delta S^\ddagger$ values of *ca.* —15 cal mol^{-1} K^{-1} were found. For the polar phosphonated acetals the high degree of orientation of the intermediates (In1) and (In2) increases the polarisability of the medium, thus further decreasing the entropy of the system.

By changing from compound (I) to (II) and (III), the rate of reaction (Table 2, Figure 2) is reduced by 45%. Since, within the limits of experimental error, the rates for (II) and (III) are equal, we may conclude that only the character of R^2, directly involved in the formation of the oxocarbonium ion in the rate-determining step, has any influence on the rate itself.

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