Reaction of Phosphonated Acetals. Part 3.[1] Acid-catalysed Hydrolysis of Diethyl 3,3-Diethoxypropylphosphonate

By **Shaul Yanai, David Vofsi,** and **Mordehai Halmann,*** The Weizmann Institute of Science, Rehovot, Israel

The kinetics of the acid-catalysed hydrolysis of diethyl 3,3-diethoxypropylphosphonate (I) have been studied in aqueous dioxan solutions, at different acid concentrations and temperatures. The reactions follow an *A*1 type mechanism with the inductive effect of the phosphonated substituent having only a minor influence. The measured second-order rate constant at 30° is 0.032 l mol^{-1} s^{-1}. Plots of log $k_{obs.}$ against log $C_{H_3O^+}$ are not linear. The deuterium solvent isotope effect k_{D_2O}/k_{H_2O} is 2.32. The energy of activation is 92 kJ mol^{-1} and the entropy of activation of 21 J mol^{-1} K^{-1}. General acid catalysis was not observed. An extremely rapid decrease in the rates of acid-catalysed hydrolysis was observed in going from compound (I) to diethyl 2,2-diethoxyethylphosphonate, (II), and to diethyl diethoxymethylphosphonate, (V). Compound (V) does not undergo regular acetal acid-catalysed hydrolysis.

PREVIOUS studies on the acid hydrolysis of phosphonated substituted acetals (II)—(IV) (based on dialkyl 2,2-diethoxyethylphosphonate) indicated the participation of the phosphoryl group in the formation of the reaction intermediates.[1,2] The phosphoryl group is properly located to the acetal carbon to form a highly stabilized intermediate (VI) with a quinone structure. This hydrogen bonded six-membered structure decreases rotational and translational degrees of freedom and increases the polarizability of the medium as observed from the thermodynamic parameters. The present kinetic study was carried out in order to check whether the participation of the phosphoryl group in a similar intermediate will persist even in the homologue (I), in which an additional CH_2 group has been inserted between the phosphoryl function and the acetal CH group.

$(EtO)_2P(O)(CH_2)_2CH(OEt)_2$

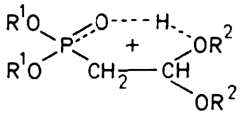
(I)

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

(II) $R^1 = R^2 = Et$
(III) $R^1 = Et$, $R^2 = Me$
(IV) $R^1 = R^2 = Me$

$(EtO)_2P(O)CH(OEt)_2$

(V)



(VI)

EXPERIMENTAL

Diethyl 3,3-*Diethoxypropylphosphonate* (I).—Compound (I) was synthesized by the Arbuzov reaction, similarly to the procedure of Razumov and Moskva,[3] from β-chlorodiethylpropionaldehyde (Aldrich) (29.9 g, 0.18 mol) and freshly distilled triethyl phosphite (50 g, 0.3 mol), during 48 h under nitrogen. The mixture was distilled under vacuum, b.p. 83—85 °C at 0.04 Torr, yielding a liquid (21.8 g, 45.3%), n_D^{20} 1.4289 (lit.,[3] 98—100 °C at 0.07 Torr; n_D^{20} 1.4290) (Found: P, 12.0. Calc. for $C_{11}H_{25}O_5P$: P, 11.6%), δ (90 MHz) 1.20 [6 H, t, *J* 7.03 Hz, $2CH_3$(acetal)], 1.32 [6 H, t, *J* 7.03 Hz, $2CH_3$(phosphonate)], 1.64—1.88 (4 H, m, PCH_2CH_2), 3.57 [4 H, quintet, *J* 7.03 Hz, $2OCH_2$-(acetal)], 4.1 [4 H, quintet, J_{PH} 3.7, J_{HH} 7.03 Hz, $2CH_2$-(phosphonate)], and 4.5 (1 H, t, *J* 5 Hz, CHO), *m/e* 103 [100%, $(C_2H_5O)CH$], 165 [8%, $(C_2H_5O)_2P(O)CH_2CH_2^+$], 223 (47%, $M - OC_2H_5$), no $M - 1$ peak observed, $\nu_{max.}$ 1 235—1 245 (P=O), 1 215, 1 160 (C–O), 1 110—1 135 (acetal), and 1 010—1 070 cm^{-1} (P–O–alkyl).

Diethyl Diethoxymethylphosphonate (V).—This was synthesized by the procedure described by Costisella and his co-workers,[4] b.p. 70—73° at 12 Torr, n_D^{25} 1.4225 (lit.,[4] 133—134° at 14 Torr, n_D^{20} 1.4255), $\nu_{max.}$ 1 251 (P=O), 1 015—1 085 (P–O–Et), 1 120, and 1 160 cm^{-1} (acetal). The ^1H n.m.r. spectrum (270 MHz) reveals a preferred ethoxy orientation at the phosphoryl group, δ 1.26 (6 H, t, *J* 7.32 Hz, 2 phosphonate CH_3), 1.36 (6 H, t, *J* 7.32 Hz, 2 acetal CH_3), 3.70 (2 H, quintet, J_{HH} 7.32, J_{PH} 9.15 Hz, P–OCH_2), 3.86 (2 H, quintet, J_{HH} 7.32, J_{PH} 10.5 Hz), 4.22 [4 H, quintet (overlap of two quartets), *J* 7.32 Hz, $COCH_2$], 4.78, and 4.76 (1 H, d, *J* 4.88 Hz, P–CH).

Kinetic Measurements.—The appearance of the carbonyl group was followed using a thermostatted block unit in a Zeiss PM QII spectrophotometer at 276 nm. The methods of calculation were described previously.[2] General acid catalysis kinetic runs were performed in a buffer acetate medium with a constant ionic strength, μ = 0.05, maintained by addition of 1M-NaCl solution.

RESULTS

Table 1 presents the observed rate constants for the kinetics of hydrolysis of acetal (I) in different concentrations of perchloric acid at 30°. Plots of log ($E_\infty - E$) *versus* time are perfectly linear (Figure a). The second-order rate constant from these measurements is (3.18 ± 0.11) × 10^{-2} l mol^{-1} s^{-1}. Figure b displays a plot of $k_{obs.}$ *versus* the molar concentration of the acid. There is a

TABLE 1

Rate constants for the hydrolysis of diethyl 3,3-diethoxypropylphosphonate in aqueous 4% dioxan at different perchloric acid concentrations at 30 °C

[Acid]/M	$10^4k_{obs.}$/s^{-1}
0.003	0.88
0.005	1.69
0.010	3.26
0.051	14.6
0.105	28.0
0.151	34.0
0.209	47.8

---

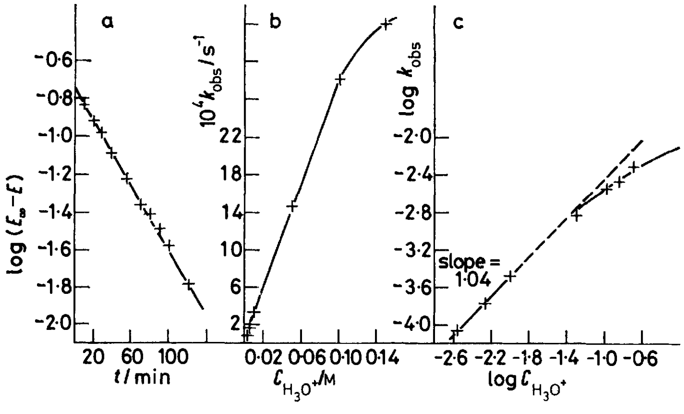
[1] Part 2, S. Yanai, D. Vofsi, and M. Halmann, preceding paper.

[2] M. Halmann, D. Vofsi, and S. Yanai, *J.C.S. Perkin II*, 1976, 1210.

[3] A. I. Razumov and V. V. Moskva, *Zhur. obschchei Khim.*, 1964, **34**, 2589.

[4] H. Gross, J. Freiberg, and B. Costisella, *Chem. Ber.*, 1968, **101** 1250; B. Costisella and H. Gross, *J. prakt. Chem.*, 1977, **319**, 8.

linear relation only at the lowest measured acid concentrations (0.002—0.01M). The same observation applies for the plot of log $k_{\text{obs.}}$ *versus* log $C_{H_3O^+}$ (Figure c). At the lowest acid concentrations the slope of the straight line portion is 1.04, but the curve slopes downwards on going to *higher acid* concentrations.



a, Plot of log ($E_\infty - E$) against time for compound (I) in aqueous 4% dioxan with 0.01M-HClO$_4$ at 30 °C; b, plot of $k_{\text{obs.}}$ against molar concentration of acid at 30 °C; c, plot of log $k_{\text{obs.}}$ against log$C_{H_3O^+}$ for compound (I) at 30 °C

Table 2 compares thermodynamic parameters for acetals (I)—(III) as calculated from Arrhenius plots. The energy of activation of acetal (I), 92 kJ mol^{-1}, is higher by *ca.* 30 kJ mol^{-1} while the entropy of activation is more positive by 125 J mol^{-1} K^{-1}. This tremendous gap may suggest different intermediate species involved in the rate-determining step. However on looking at the site of the reaction by means of the deuterium solvent isotope effect we do not observe any meaningful difference. The observed k_{D_2O}/k_{D_2O} value for acetal (I) is 2.32 ± 0.03, which is not altered by a ten-fold variation in the sulphuric acid concentration (Table 3).

TABLE 2

Thermodynamic functions calculated for the hydrolysis of (I) in 0.0055M-HClO$_4$ and (II) and (III) in 0.5M-HClO$_4$

Compound	10^4k_2/l mol^{-1} s^{-1} 30°	40°	50°	E_a/K J mol^{-1}	$\Delta S^\ddagger$/J mol^{-1} K^{-1}
(I)	300.0	1 040.0	2 730.0	91.7 ± 1.2	19.7 ± 0.8
(II)	13.5	28.8	87.4	62.4 ± 2.6	−104.6 ± 2.0
(III)	4.7	7.2	11.1	62.4 ± 2.6	−113.0 ± 1.4

TABLE 3

Deuterium solvent isotope effects for the hydrolysis of acetal (I) in sulphuric acid at 30°

[Acid]/M	$10^4k_{D_2O}$/s^{-1}	$10^4k_{H_2O}$/s^{-1}	k_{D_2O}/k_{H_2O}
0.0049	5.24	2.23	2.35
0.0049	4.90	2.14	2.29
0.0453	30.90	13.7	2.26
0.0453	31.60	13.9	2.28

TABLE 4

Observed rate constants in buffered acetate solutions (pH 3.95) and constant ionic strength μ 0.05 for the hydrolysis of acetal (I) at 45°

[HA]/M	[A]/M	$10^5k_{\text{obs.}}$/s^{-1}
0.300	0.0500	1.8
0.225	0.0375	2.0
0.150	0.0250	2.0
0.075	0.0125	2.1

Table 4 summarizes the data for the general acid catalysis runs. It reveals a relatively constant rate of 1.06 × 10^{-5} s^{-1} with a 7% deviation upon a four-fold dilution of the acid concentration.

DISCUSSION

The rates of acid-catalysed hydrolysis of the propylphosphonate (I) are *ca.* 40 times larger than those of the corresponding ethylphosphonate (II), which contains one methylene group less in the aliphatic chain. As seen in Figure b there is no appreciable contribution by any neutral reaction. Although the very fast rates did not allow us to consider Hammett acidity functions, we see that there does not exist a linear correlation between log $k_{\text{obs.}}$ and log $C_{H_3O^+}$ (Figure c). This observation excludes the probability of an *A*2 mechanism.[5] The large discrepancy in the thermodynamic parameters between acetal (I) and acetals (II)—(IV) does not require that the former takes a route different from the *A*1 mechanism demonstrated for the latter series. Actually the measured energy and entropy of activation for the propylphosphonate (I) resemble very much the classic values found for simple linear acetals.[6] The low results for the thermodynamic values of acetals (II) and (III) had been explained by the participation of the phosphoryl group in the formation of the intermediates.[2] Its location in these cases allows the formation of thermodynamically stable features through a hydrogen bridge to the acetal oxygen. Thus the return to ' normal ' values of simple acetals achieved by insertion of an additional methylene group between P=O and the acetal site confirms previous ideas.

It has been proposed that *A*1 mechanisms are characterized by k_{D_2O}/k_{H_2O} values in the range 2.5—3.3,[5] while values of 1.7—2.4 were found for cases of rate-determining water attack.[7] For acetals (II) and (III) the observed values were 2.4 and 2.8, respectively.[1] The ratio of k_{D_2O}/k_{H_2O} of 2.32 ± 0.03 for acetal (I) is close to these values and far enough from the usual ratios observed for hydrolysis of acetals by an *A*2 mechanism. Hence we may say that although the present (*A*1) type reaction goes through different intermediates, there are no differences in the pathways of hydrogen transfer occurring at the acetal site.

Kinetic experiments performed in buffer acetate solutions (Table 4) supply further evidence for a first-order specific hydronium ion catalysed reaction for acetal (I). The observed rate constant, 1.96 × 10^{-5} s^{-1}, is almost constant (within 7%) upon a four-fold dilution of the acetic acid concentration.

The diethoxyphosphoryl group shows moderately electron-attracting properties.[8] Using the σ^*–ρ^* relationship established by Taft for the ionization of

---

[5] E. H. Cordes and H. G. Bull, *Chem. Rev.*, 1974, **74**, 581.

[6] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 27.

[7] R. L. Schowen, *Progr. Phys. Org. Chem.*, 1972, **9**, 275.

[8] L. D. Freedman and H. H. Jaffé, *J. Amer. Chem. Soc.*, 1955, **77**, 920.

carboxylic acids, Martin and Griffin were able to calculate σ^* values for the substituent groups CH_2PL_3 where L is O, S, alkyl, aryl, and alkoxy.[9] Thus for $CH_2P(O)(OEt)_2$ σ^* has been calculated as 0.78, which establishes the group as an electron acceptor comparable with C_6H_5 (σ^* 0.60) and $CH_2CO_2C_2H_5$ (σ^* 0.71). The interposition of a methylene group reduces the inductive effect by a factor of 2.8.[10] Thus σ^* for the substituent group of acetal (I), $CH_2CH_2P(O)(OEt)_2$, is *ca.* 0.28. This value suggests that its inductive effect is of the same order of magnitude as that of the $C_6H_5CH_2$ group (σ^* 0.22). In their investigation of the acid-catalysed hydrolysis of 24 simple linear acetals Kreevoy and Taft [11] found that the rates are directly proportional to the polar substituent constants, σ^*, and to C–H resonance effects contributed by α-hydrogen atoms to the acetal centre. These effects are additive and independent. Thus for $C_6H_5CH_2CH(OEt)_2$, k_2 is 8.7×10^{-3} l mol^{-1} s^{-1}, which is within 0.19 log units of the predicted value. Under the same conditions our observed k_2 for acetal (I) is 1.6×10^{-2} l mol^{-1} s^{-1}, which deviates by only 0.29 log units from the calculated value. This result makes it reasonable to exclude any steric or resonance effects of d_π–p_π bonding. A similar conclusion had been reached previously for the hydrolysis of the ethylphosphonate acetals. The two-fold increase in the expected rate value may be attributed to higher susceptibility to hyperconjugation effects in a medium strongly polarized by the phosphoryl group.[12]

Diethyl diethoxymethylphosphonate (V) was found not to undergo hydrolysis in 5% concentrated hydrochloric acid at room temperature during 60 days, as seen from its unchanged n.m.r. spectra. The predicted rate constant, taking into account Kreevoy and Taft's parameters, is 7.9×10^{-11} l mol^{-1} s^{-1}. This explains why this compound does not react as expected even under drastic conditions. Instead P–C bond splitting was reported [13,14] resulting in diethyl phosphate and ethyl formate.

We thank Mrs. V. Katzir for technical assistance with the kinetic measurements.

[7/1506 *Received*, 19*th August*, 1977]

---

[9] D. J. Martin and C. E. Griffin, *J. Org. Chem.*, 1965, **30**, 4034.

[10] R. W. Taft, jun., 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Wiley, New York, 1956, ch. 13.

[11] M. M. Kreevoy and R. W. Taft, jun., *J. Amer. Chem. Soc.*, 1955, **77**, 5590.

[12] G. Aksnes, *Acta Chem. Scand.*, 1960, **14**, 1515.

[13] A. I. Razumov and V. V. Moskva, *Zhur. obschchei Khim.*, 1965, **35**, 1595.

[14] J. Gloede and B. Costisella, *J. prakt. Chem.*, 1971, **313**, 277.