# Reaction of Phosphonated Acetals. Part 2.[1] Synthesis and Acid-catalysed Hydrolysis of the Cyclic Acetals 2-Diethylphosphonomethyl-1,3-dioxolan, 2-Diethylphosphonomethyl-1,3-dioxan, and Bis-*O*-(diethylphosphonoethyl)pentaerythritol

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Phosphonated cyclic acetals were prepared by transacetalation of diethyl 2,2-diethoxyethylphosphonate (I) with ethylene glycol, propane-1,3-diol, or pentaerythritol, to form 2-diethylphosphonomethyl-1,3-dioxolan (III), 2-diethylphosphonomethyl-1,3-dioxan (IV), and bis(diethylphosphonomethyl)pentaerythritol (V), respectively. The structures of the products were confirmed by $^1$H and $^{13}$C n.m.r. and by mass and i.r. spectrometry. The kinetics of acid-catalysed hydrolysis of the cyclic acetals were measured in water containing 4% dioxan (v/v) as a function of acid concentration and temperature, and with respect to the deuterium solvent isotope effect. The results are compared with those of the open-chain acetals (I) and diethyl 2,2-dimethoxyethylphosphonate (II). The Zucker–Hammett hypothesis gives for compounds (III)—(V) a linear dependence of log $k_{obs}$ on log $C_{H_3O^+}$, with slopes between 1.7 and 3.2. The Bunnett *w* parameters have values of 0.7—2.7, and $k_{D_2O}/k_{H_2O}$ is *ca.* 2. The reaction of the dioxan derivative (IV) is five times slower than that of the corresponding dioxolan derivative (III). These criteria are not in accordance with an *A*1 reaction, as found for acetals (I) and (II), nor do they agree too well with an *A*2 reaction. In view of these results we tentatively suggest for the cyclic acetals (III) and (IV) an $A$–$S_E2$ mechanism. In the proposed mechanism the initial protonated substrate is partially stabilised by hydrogen bonding between the acetal oxygen and the phosphoryl oxygen atoms. As a result the oxonium ion is involved in a reversible reaction and hence proton transfer to the oxygen atom is the rate-determining step of the hydrolysis.

THE acid-catalysed hydrolysis of several open-chain phosphonated acetals, diethyl 2,2-dialkoxyethylphosphonates (I) and (II), has been shown to have the characteristic features of an *A*1 reaction, *i.e.* a linear relationship of log *k* with $-H_0$ (slope 0.98) and a deuterium solvent isotope effect $k_{D_2O}/k_{H_2O} = 2.8$ [for (II)].[1] In the present work this study has been extended to the cyclic acetals (III)—(V) in order to find out to what extent the rates and mechanism of hydrolysis are affected by constraining the acetal methine group into a ring structure. Kinetic data will be treated using the Zucker–Hammett hypothesis [2] and the parameters of Bunnett.[3]

## EXPERIMENTAL

N.m.r. spectra were taken on Bruker HFX10 and WH-270 instruments [references: TMS (internal) for $^1$H and $^{13}$C; 85% $H_3PO_4$ (external) for $^{31}$P] and i.r. spectra on a Perkin-Elmer 237B instrument as 0.05M-chloroform solutions or as KBr (1%) pellets. Mass spectra were taken on a Varian-Mat 731 mass spectrometer. T.l.c. was performed on silica gel plates on n-butanol–acetic acid–water (6 : 3 : 1). Visualisation was performed by spraying for 1,2-diols with sodium periodate–benzidine [4a] and for phosphonates by ammonium molybdate–perchloric acid.[4b] Ethylene glycol and propane-1,3-diol (B.D.H.) were freshly distilled before reaction. Pentaerythritol (B.D.H.) was used as received.

2-*Diethylphosphonomethyl*-1,3-*dioxolan* (III).—Compound (III) was prepared by transacetalation between compound (I) (25.4 g, 0.1 mol) and ethylene glycol (6.2 g, 0.1 mol), in the presence of concentrated hydrochloric acid (10 ml), at room temperature, with magnetic stirring, for 24 h. The product was isolated by vacuum distillation as an *oil* (7.9 g, 35%), b.p. 79—80° at 0.05 Torr; $n_D^{25}$ 1.445 (Found: P, 13.7. $C_8H_{17}O_5P$ requires P, 13.8%); $\delta_H$ 1.23 (6 H, t, *J* 7.03

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

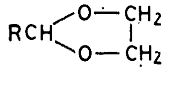
[2] L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2791.

[3] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, (*a*) 4956; (*b*) 4968; (*c*) 4973; (*d*) 4978.

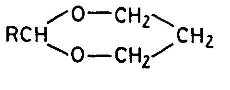
[4] 'Thin Layer Chromatography,' ed. E. Stahl, Springer-Verlag, Berlin–Heidelberg–New York, 1969, 2nd edn., (*a*) p. 885, no. 158; (*b*) p. 886, no. 166.

Hz), 2.10 (2 H, dd, $J_{PH}$ 18.6, $J_{CH_2CH}$ 5.1 Hz, $PCH_2C$), 3.81—4.02 (4 H, $A_2B_2$ system, $J$ 9 Hz, $OCH_2CH_2O$), 4.03 (4 H, quintet, $J_{PH}$ 3.7, $J_{CH_3CH_2}$ 7.03 Hz, $POCH_2C$), and 5.06 [1 H, quartet (2 t), $J_{PH}$ 4.8, $J_{CH_2CH}$ 5.1 Hz, CHO]; $\delta_C$ 16.25, 16.51 ($CH_3$), 29.06, 35.21 ($J$ 139.16 Hz, $P–CH_2$), 61.75, 61.49 ($J$ 5.86 Hz, $POCH_2$), 64.79 ($OCH_2CH_2O$), and 99.75 (CHO); $\delta_P$ −25.9; *m/e* 224 ($M^+$, 1.7%), 73 ($C_3H_5O_2^+$, 100), and 151 ($M$ − 73, 15); 1 200 (P=O), 1 160 (O·CH·O), and 1 085 $cm^{-1}$ (P–O–alkyl).

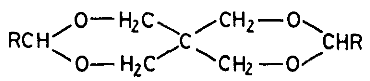
$(EtO)_2P(O)CH_2CH(OR)_2$
(I) R = Et
(II) R = Me



(III)



(IV)



(V)

R = $(C_2H_5O)_2P(O)CH_2$

2-*Diethylphosphonomethyl*-1,3-*dioxan* (IV).—Compound (IV) was similarly prepared by reaction of compound (I) (25.4 g, 0.1 mol) with propane-1,3-diol (7.6 g, 0.1 mol) in the presence of concentrated HCl (10 ml) for 4 h, yielding an *oil* (18.3 g, 78%), b.p. 96—98° at 0.07 Torr; $n_D^{25}$ 1.448 (Found: P, 13.15. $C_9H_{19}O_5P$ requires P, 13.0%), $\delta_H$ 1.31 (6 H, t, $J$ 7.04 Hz, $CH_3$), 2.16 (2 H, dd, $J_{PH}$ 18.49, $J_{CH_2CH}$ 5.57 Hz, $P–CH_2–C$), 3.64—4.1 (6 H, m, $–O[CH_2]_3O$), 4.09 (4 H, quintet, $J_{PH}$ not determined, $J_{CH_3CH_2}$ 7.04 Hz, $POCH_2C$), and 4.9 [1 H, quartet (2t), $J_{PH}$ 5.57, $J_{CH_2CH}$ 5.57 Hz, CHO], $\delta_C$ 16.44, 16.18 ($CH_3$), 25.44 (CCC), 36.44, 30.16 ($J$ 142.09 Hz, $P–CH_2$), 61.30, 61.56 ($J$ 5.86 Hz, $POCH_2$), 66.67 ($O–CH_2–C–CH_2–O$), and 97.68 (CHO), $\delta_P$ −26.4; *m/e* 237 ($M$ − $1^+$, 2.5%), 87 ($CH_2C_4H_7O_2^+$, 100), 151 ($M$ − 87, 10); $\nu_{max.}$ 1 220 (P=O), 1 100 (O·C·O), and 1 035 $cm^{-1}$ (P–O–alkyl).

*Bis*-O-(*diethylphosphonomethyl*)*pentaerythritol* (V).—Compound (V) was similarly prepared by reaction of compound (I) (6 g, 0.024 mol) with pentaerythritol (2.7 g, 0.020 mol) and concentration HCl (10 ml) for 30 min. After neutralisation the mixture was extracted with toluene (150 ml), which yielded upon evaporation, a solid. Recrystallisation from ethyl acetate–hexane (1 : 3) yielded shiny *crystals* (2.4 g, 30%), m.p. 101—102° (Found: C, 44.2; H, 7.95; P, 12.7. $C_{17}H_{34}O_{10}P_2$ requires C, 44.3; H, 7.5; P, 13.5%); $\delta_H$ 1.31 (12 H, t, $J$ 7.03 Hz, $CH_3$), 2.18 (4 H, dd, $J_{PH}$ 18, $J_{CH_2CH}$ 5 Hz, $PCH_2C$), 3.3—3.6 (8 H, AB, $J$ 8.3 Hz, $C[CH_2]_4$), 4.09 (8 H, quintet, $J_{PH}$ 3.8, $J_{CH_2CH_3}$ 7.03 Hz, $POCH_2C$), 4.8 [2 H, quartet (2t), $J_{PH}$ 6.16, $J_{CH_2CH}$ 5.42 Hz, CHO]; $\delta_C$ 16.18 ($CH_3$), 31.98 (quaternary C), 29.65, 35.99 ($J$ 143.55 Hz, $PCH_2$), 61.92, 61.88 ($J$ 5.86 Hz, $POCH_2CH_3$), 70.56, 69.90 ($CCH_2O$), and 98.26 (CHO); $\delta_P$ −26; *m/e* 460 ($M^+$, 14.3%), 459 (19), 323 [$M$ − (I)$P(OC_2H_5)_2$, 24], and 87 (100); $\nu_{max.}$ 1 230 (P=O), 1 155, 1 120 (O·C·O), and 1 030 $cm^{-1}$ (P–O–alkyl).

*Kinetic Measurements*.—The rates of reaction were followed and calculated as previously described.[1] The measurements were performed at λ 286 nm. Constant ionic strength was accomplished by addition of sodium perchlorate (Fluka AG, puriss) up to 6M. Deuteriated sulphuric acid was prepared by mixing 98% sulphuric acid (AnalaR; B.D.H.) with deuterium oxide (99.7%; Carl Roth).

## RESULTS

At low acid concentrations (0.5—2M) and moderate temperatures (35°) the reactions of the 1,3-dioxans do not follow simple first-order kinetics. On the other hand the 1,3-dioxolans observe first-order kinetics over the range of acidities and temperature tested. As shown in Figure 1(a), a plot of log($E_\infty$ − $E$) *versus* time for acetal (IV) indicates two linear portions, for a slow and a fast reaction. At higher acid concentrations (>2M) the fast reaction component practically disappears and only one component

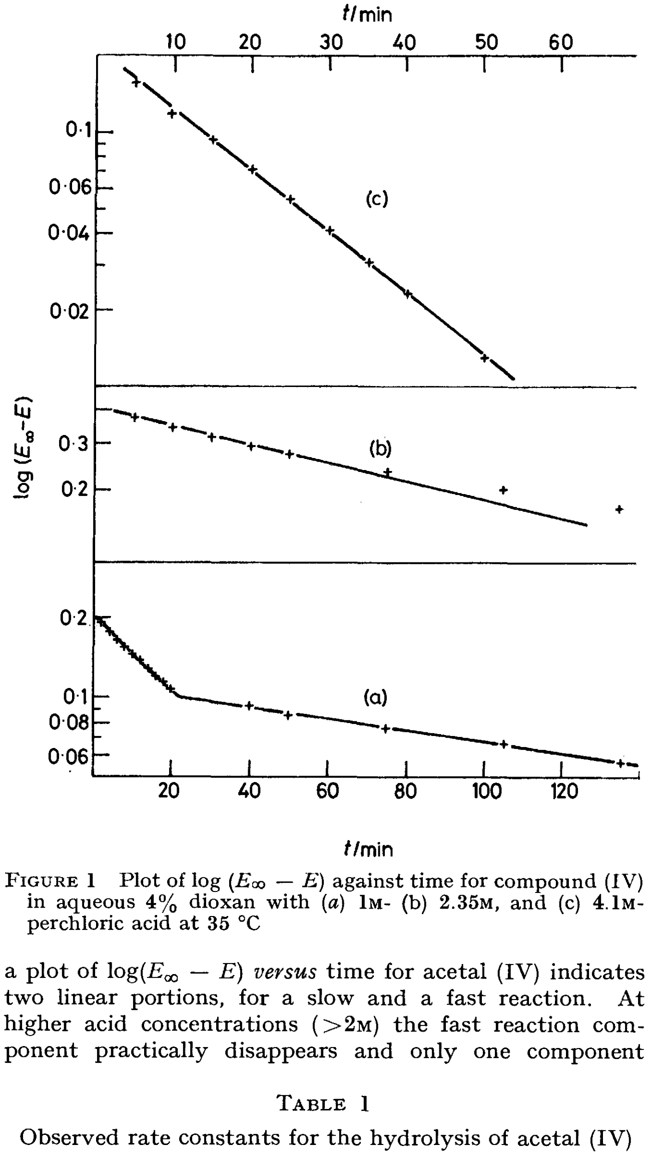


FIGURE 1 Plot of log ($E_\infty$ − $E$) against time for compound (IV) in aqueous 4% dioxan with (*a*) 1M- (b) 2.35M, and (c) 4.1M-perchloric acid at 35 °C

TABLE 1

Observed rate constants for the hydrolysis of acetal (IV) in perchloric acid at 35 and 45°

| $[HClO_4]$/M | $10^4k_{obs}/s^{-1}$ at 35° | | $10^4k_{obs}/s^{-1}$ at 45° | |
|---|---|---|---|---|
| | $k'$ | $k''$ | $k'$ | $k''$ |
| 1.0 | 2.18 | 0.444 | 2.12 | 0.791 |
| 1.6 | 2.20 | 0.531 | | 1.65 |
| 2.0 | 2.62 | 0.955 | | 2.89 |
| 2.35 | | 1.34 | | 3.85 |

obeying first-order kinetics is observed, as shown in Figure 1(c). By increasing the temperature single component kinetics are observed even for runs at concentrations <2M. In Table 1, two values of rate constants, $k'$ and $k''$, are given for the case of compound (IV), for those runs showing the two component kinetics.

First-order rate constants $k_{obs}$ for the hydrolysis of the cyclic phosphonated acetals (III) and (IV) at 45 and 25° with $\mu$ 6 as a function of perchloric acid concentration are presented in Table 2, which also includes Hammett acidity functions $-H_0$ and values of log $a_{H_2O}$. The rate constants presented in Table 2 for acetal (V) are for runs at 65° and without addition of sodium perchlorate. Presentation of log $k_{obs} + H_0$ *versus* log $a_{H_2O}$ (Figure 2) results in a plot typical for such hydrolyses, which has been termed by Bunnett 'J shaped'.[3a] The straight line portion of this plot corresponds to a slope $w$ of 1.53 ± 0.01 for acetal (III) and 1.03 ± 0.01 for acetal (IV). Using the experimental data at 45° (Table 2) without the addition of sodium perchlorate, in combination with $H_0$ and water activities[1] at 25° one gets $w$ 2.69 ± 0.02 and 0.7 ± 0.05 for acetals (III) and (IV), respectively. Treatment of the data by the Zucker–Hammett hypothesis shows very good linear correlations of log $k_{obs}$ with log $C_{H_3O^+}$ (Figure 3). The respective slopes are 1.69 ± 0.02 for acetal (III), 1.91 ± 0.02 for acetal (IV), and 3.17 ± 0.1 for acetal (V).

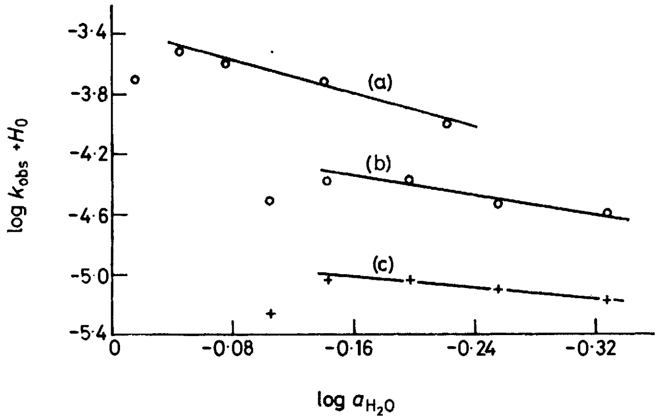


FIGURE 2 Plot of (log $k_{obs}$ + $H_0$) against log $a_{H_2O}$ for compound (III) at 45 °C (a) and 25 °C (b) and compound (IV) at 25 °C (c) at different perchloric acid concentrations

Activation parameters for acetals (III) and (IV) derived from rate measurements in 2M-perchloric acid at several temperatures and at 3.89M-sulphuric acid for acetal (V), are

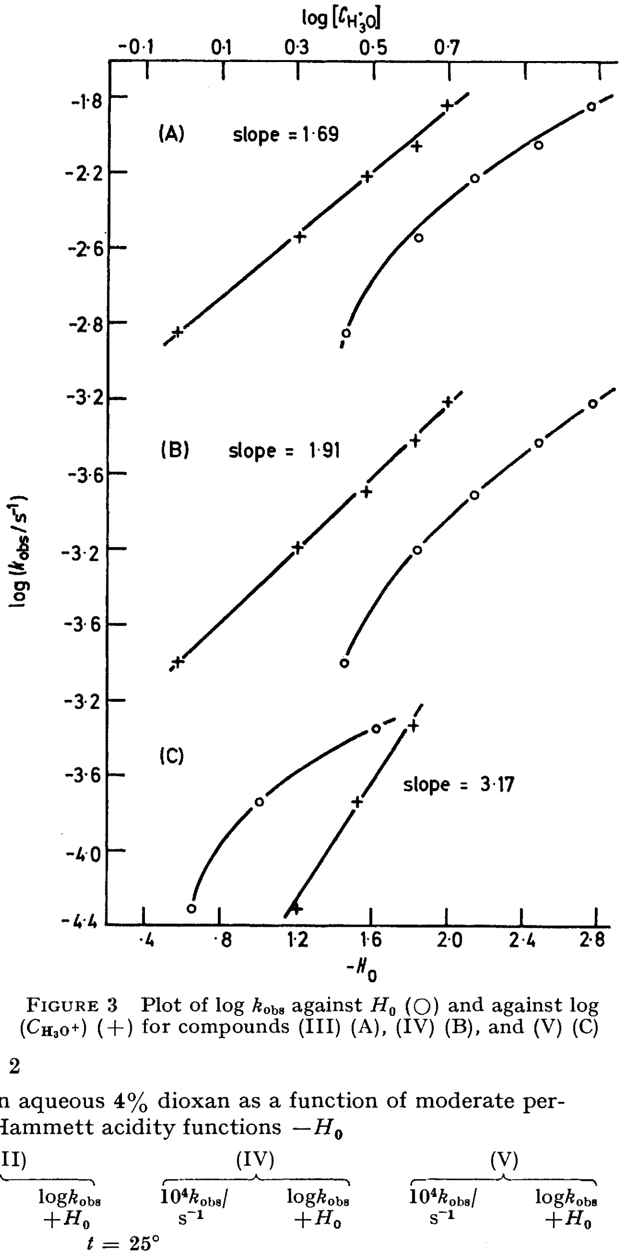


FIGURE 3 Plot of log $k_{obs}$ against $H_0$ (○) and against log ($C_{H_3O^+}$) (+) for compounds (III) (A), (IV) (B), and (V) (C)

TABLE 2

Rate constants for the hydrolysis of acetals (III)—(IV) in aqueous 4% dioxan as a function of moderate perchloric acid concentrations and the Hammett acidity functions $-H_0$

| | | | | (III) | | (IV) | | (V) | |
|---|---|---|---|---|---|---|---|---|---|
| [Acid]/M | [NaClO$_4$]/M | $-H_0$ | $-\log a_{H_2O}$ | $10^4k_{obs}$/s$^{-1}$ | $\log k_{obs} + H_0$ | $10^4k_{obs}$/s$^{-1}$ | $\log k_{obs} + H_0$ | $10^4k_{obs}$/s$^{-1}$ | $\log k_{obs} + H_0$ |
| | | | | $t$ = 25° | | | | | |
| 0.96 | 5.04 | 1.46 [a] | 0.105 [b] | 8.89 | −4.51 | 1.57 | −5.26 | | |
| 2.04 | 3.96 | 1.85 | 0.143 | 28.8 | −4.39 | 6.42 | −5.04 | | |
| 3.05 | 2.95 | 2.15 | 0.197 | 60.8 | −4.37 | 12.8 | −5.04 | | |
| 4.08 | 1.92 | 2.48 | 0.256 | 88.8 | −4.53 | 24.0 | −5.10 | | |
| 5.00 | 1.00 | 2.77 | 0.328 | 144. | −4.61 | 38.5 | −5.18 | | |
| 2.01 | 0 | 0.642 [c] | 0.045 [c] | 1.79 | −4.39 | 0.386 | −5.05 | | |
| | | | | $t$ = 45 °C | | | | $t$ = 65 °C | |
| 1.0 | 0 | 0.175 [c] | 0.018 [c] | 2.96 | −3.70 | 1.01 | −4.17 | | |
| 2.01 | 0 | 0.642 | 0.045 | 13.1 | −3.52 | 2.82 | −4.19 | 0.49 | −4.95 |
| 2.94 | 0 | 1.09 | 0.078 | 31.2 | −3.59 | 6.51 | −4.28 | 1.80 | −4.83 |
| 4.08 | 0 | 1.635 | 0.141 | 79.7 | −3.73 | 24.0 | −4.25 | 4.72 | −4.96 |
| 5.07 | 0 | 2.105 | 0.222 | 126.0 | −4.00 | 78.0 | −4.21 | | |

[a] In accord with ref. 7. [b] In accord with ref. 8. [c] In accord with ref. 1.

TABLE 3

Thermodynamic functions calculated for the hydrolysis of acetals (III) and (IV) in 2M-$HClO_4$, and (V) in 3.89 M-$H_2SO_4$

| Compound | $10^4k_2$/l mol s$^{-1}$ | | | | | $E_a$/ kJ mol$^{-1}$ | $\Delta H^‡$/ kJ mol$^{-1}$ | $\Delta S^‡$/ J mol$^{-1}$ K$^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| | 25 °C | 35 °C | 45 °C | 55 °C | 65 °C | | | |
| (III) | 0.891 | 2.25 | 6.53 | 15.5 | | 79.0 | 76.4 | −66.8 |
| (IV) | 0.193 | 0.475 | 1.40 | 3.51 | | 80.1 | 77.5 | −75.7 |
| (V) | | | 0.177 | 0.41 | 0.825 | 71.9 | 69.1 | −119.5 |
| (I) [a] | 4.8 | 11.8 | 22.4 | | | 62.3 | 59.7 | −104.5 |

[a] Ref. 1.

TABLE 4

Solvent deuterium isotope effects for acetals (III)—(V) in 4M-$H_2SO_4$

| Compound | $10^4k_2$/l mol$^{-1}$ s$^{-1}$ | | |
|---|---|---|---|
| | $k_{H_2O}$ | $k_{D_2O}$ | $k_{D_2O}/k_{H_2O}$ |
| (III) [a] | 5.97 | 11.2 | 1.88 |
| (IV) [a] | 1.07 | 2.25 | 2.10 |
| (V) [b] | 0.177 | 0.29 | 1.64 |

[a] At 35°. [b] At 45°.

presented in Table 3 and Figure 4. All activation energies are closely grouped in the range 72—80 kJ mol$^{-1}$. The entropy of activation for the acetal derived from pentaerythritol is *ca.* 50 J mol$^{-1}$ K$^{-1}$ more negative than the related values found for the simpler cyclic acetals, thus pointing to the higher degree of order involved.

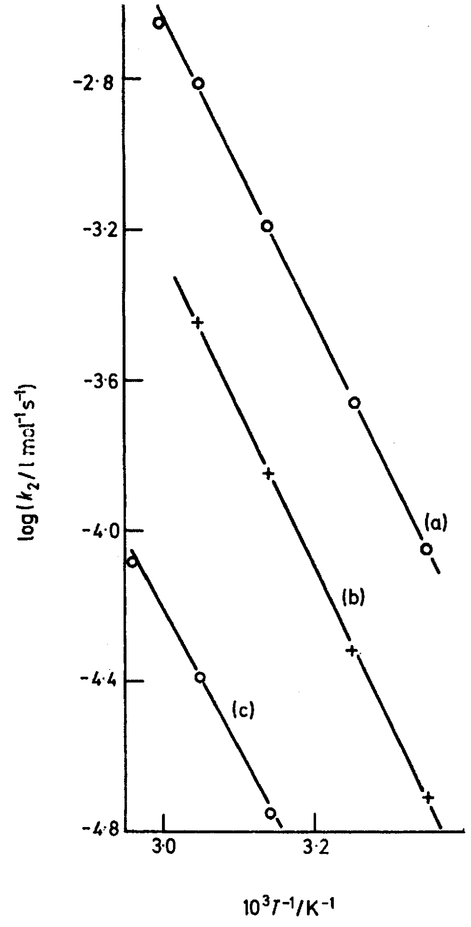


FIGURE 4 Plot of log $k_2$ against 1/*T* for compounds (III) (a), (IV) (b), and (V) (c)

The deuterium solvent isotope effect measured in 4M-sulphuric acid at 35° is presented in Table 4. $k_{D_2O}/k_{H_2O}$ is *ca.* 2 for acetals (III) and (IV) and somewhat smaller, 1.64 for acetal (V).

DISCUSSION

Two step kinetics had been observed in the hydrolysis of many substituted 1,3-dioxans.[5] The effect was attributed to the formation of the hemiacetal, the relative concentration of which increases at equilibrium with decreasing temperature.

Wyatt [6] has shown that $H_0$ is a unique function of the water activity for several strong acids. The Bunnett treatment is based on this statement and using the $H_0$ data presented by Paul and Long [7] for $\mu$ 6 and the corresponding water activities from Yates and Wai.[8]

For mineral acids, the variation of $H_0$ with temperature in the range 20—80° is very small,[9] $dH_0/dt$ 0.003. It is recognized that the variation of *w* with temperature keepts its values inside the limits of criteria of mechanism as suggested by Bunnett.[10] Thus the range of our observed *w* values falls into the mechanistic category in which water is involved as a nucleophile in the rate-determining step of the acid-catalysed reactions, *i.e.* an *A*2 reaction. For the linear phosphonated acetals (I) and (II) the *w* values have been found to be typical for an *A*1 reaction, *w* —0.1. For these compounds log $k_{obs}$ *versus* $-H_0$ was linear with a unit slope.[1] The same plot for the cyclic acetals (III)—(V) slopes downwards in all cases and thus the *A*1 mechanism of hydrolysis previously reported for the linear acetals cannot be extended to the cyclic acetals (III)—(V).[7] Although in this case we get linearity for log $k_{obs}$ *versus* log $C_{H_3O^+}$ the resulting slopes (1.6—3.2) deviate strongly from the unit value demanded by the Zucker–Hammett hypothesis [2] for *A*2 mechanisms. Attempts to clarify the mechanism by finding *w** values failed, since neither log $k_{obs}$ − log $C_{H_3O^+}$ nor log $k_{obs}$ − log $C_{H_3O^+}$ − $H_0$ *versus* log $a_{H_2O}$ are linear.

The energies of activation for acetals (III) and (IV) are higher by *ca.* 17 kJ mol$^{-1}$ compared with the open acetal (I), while the entropy parameters are more positive by *ca.* 30 J mol$^{-1}$ K$^{-1}$. These results do not correspond to a previous statement [11] that ring closure has very little effect upon these constants. However,

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[6] P. A. H. Wyatt, *Discuss. Faraday Soc.*, 1957, **24**, 162.

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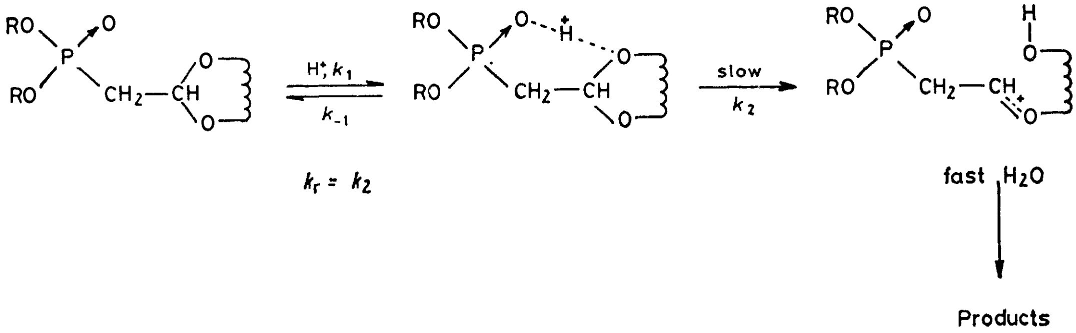
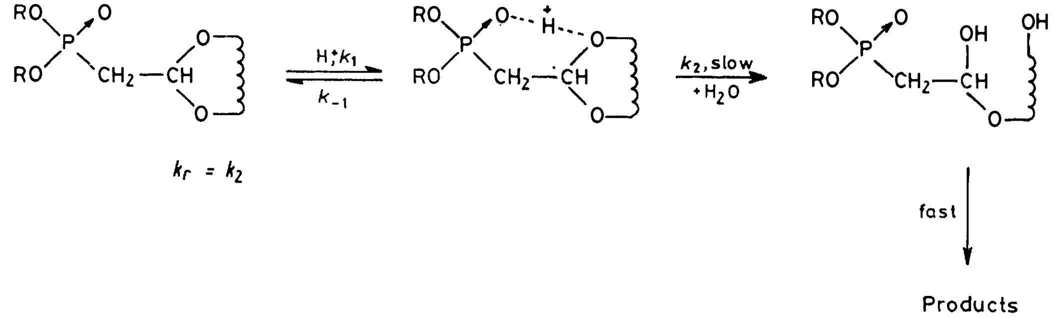
[10] C. H. Rochester, 'Acidity Functions,' Academic Press, London and New York, 1970, p. 120.

[11] O. Ceder, *Arkiv. Kemi*, 1954, **6**, 523.

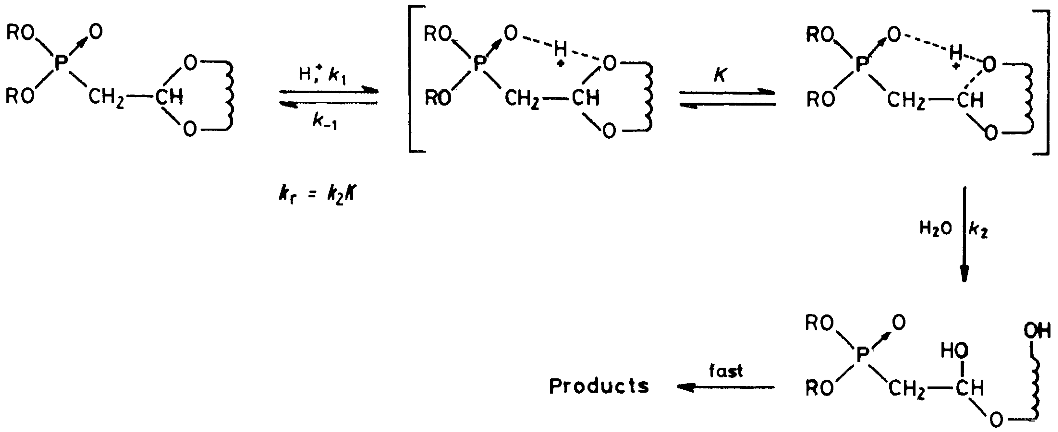
by comparison with simple alkyl substituted linear acetals[12] as well as with similar 1,3-dioxolan[13] and 1,3-dioxan[5] systems, it seems clear that the activation energies for both linear and cyclic phosphonated acetals are lower by 21—35 kJ mol$^{-1}$. We have previously suggested[1] that there is stabilisation of the transition state due to the participation of the phosphoryl group in the delocalisation of charge by hydrogen bond to the acetal oxygen. The definitively different values of activation entropies for the cyclic phosphonated acetals support the assumption of a probable change in mechanism. Their values lie in the range expected for $A2$ or $A$–$S_E2$ reactions.[14] The mechanistic criteria applied exclude the possibility of an $A1$ pathway for these compounds (Scheme 1) but they do not distinguish between $A2$ (Scheme 2) and $A$–$S_E2$ mechanisms (Scheme 3). The deuterium solvent isotope effects are frequently similar for $A$–$S_E2$ and $A2$ hydrolyses.[15] It has been proposed that $A1$ mechanisms are characterised by $k_{D_2O}/k_{H_2O}$ values in the range 2.5—3.3,[16a] while values of 1.7—2.4 were found for cases of rate-determining water attack.[16b] Fife narrows the $A2$ range of $k_{D_2O}/k_{H_2O}$ to 1.3—1.7.[17] However, as suggested by Cordes and Bull, the kinetic solvent deuterium isotope effects for $A$–$S_E2$ mechanisms are expected to be <2.3, whether or not



Scheme 1



Scheme 2



Scheme 3

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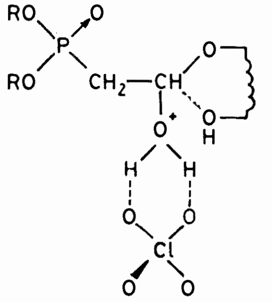
general acid catalysis is experimentally observable.[16a] Thus the values of 1.88—2.10 found in this study for acetals (III) and (IV) (Table 4) and 1.64 for acetal (V) lie in between the normal ranges of values just presented. Such values suggest that the proton transfer is incomplete, but they are high enough to assume a certain proton transfer to the oxygen. The facts can be explained if there is a concerted proton attack on oxygen and carbon–oxygen bond breaking as in $A$–$S_E2$ reactions. $A1$ mechanisms involve a carbonium ion like transition state. In our case the phosphoryl group is properly located to share the attacking proton through hydrogen bond with the oxygen. Due to this barrier the newly formed hydroxy-group is still part of the same molecule as the carbonium ion centre, which is not the case with the linear phosphonated acetals. Hence in the transition state there is a reversible reaction of the carbonium ion which does not allow the development of an $A1$ reaction and which results in an incomplete proton transfer effect (Scheme 3). Capon and Thacker[18] suggested such a reversibility in the formation of the carboxonium ion in the case of acid hydrolysis of glucofuranosides. However by applying similar mechanistic approaches the authors considered an $A2$ reaction, in which the alcohol molecule is displaced by $H_2O$. Tentative $A2$ mechanisms have been assumed[17] for acetal hydrolysis in some studies which were inconsistent with $A1$ mechanisms, although it is not possible by these data to distinguish them from the $A$–$S_E2$ mechanism.

From Table 2 we see that the rate constants for acetals (III) and (IV) at $\mu$ 6 are 16 times greater than the observed values for runs without constant ionic strength. On considering the hypothesis of Olson and Tong[19] one can look upon these rate effects as a result of preferred orientation of $H_2O$ molecules toward the positively charged transition state under the influence of the anion. This possibility suggests solvent involvement in the rate-determining step (Scheme 4). This picture is supported by the $w$ values but does not fit the results of the Zucker–Hammett treatment, and the values of $k_{D_2O}/k_{H_2O}$, and it does not consider the participation of the phosphoryl group. The participation of the phosphoryl group in the transition state results from its proper location to form a semiquinone ring through a hydrogen bond to the alkoxy leaving group. In the hydrolysis of $(EtO)_2P(O)CH_2CH_2CH(OEt)_2$ we have found[20] a strictly classic $A1$ reaction, including no general acid catalysis. Moreover, in studies of salt effects on the hydrolysis of acetals and orthoesters the following order of decreasing sensitivity to the salt effect was observed:[15] orthoacetate > orthoformate > acetal.



SCHEME 4

This sequence is inverse to increasing carbonium ion stability. There is thus a mechanistic change from $A1$ to $A$–$S_E2$ in going from acetal to orthoester. For the $A$–$S_E2$ hydrolysis of orthoesters, $k_{D_2O}/k_{H_2O}$ is between 2.2 and 2.4.[21,22] Smaller values, 1.4, were reported for the hydrolysis of orthocarbonates.[23] Thus it seems more attractive to assume that in passing from linear to cyclic phosphonated acetals there is a mechanistic change from $A1$ to $A$–$S_E2$. Hydrolytic $A$–$S_E2$ reactions for 1,3-dioxolans have been reported for compounds with highly electronegative substituents on the acetal carbon such as a trichloromethyl group[24] and with a few acylic compounds derived from trihalogenoethanols.[25]

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