# Acylphosphonate hemiketals—formation rate and equilibrium. The electron-withdrawing effect of dimethoxyphosphinyl group

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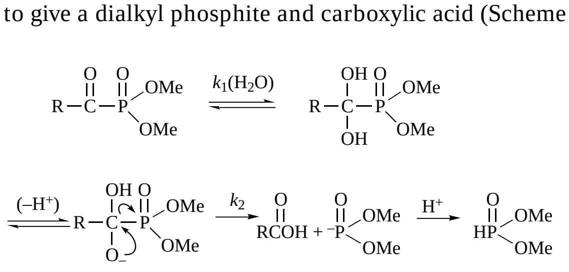
**Examination of alcoholic solutions of dimethyl acetylphosphonate (1) and dimethyl benzoylphosphonate (2) by $^{31}P$ NMR spectroscopy reveals the presence of considerable amounts of hemiketals. Because of the great difference between the $^{31}P$ chemical shifts of acylphosphonates (*ca.* 0 ppm) and their hemiketals (17–21 ppm), $^{31}P$ NMR spectroscopy is a uniquely suitable method for studying the rates and equilibria of hemiketal formation of acylphosphonates with different alcohols. The equilibrium constants $K_f$, $K'_f$ ($K'_f = K_f$[ROH]), pseudo-first-order rate constants $k'_f$, the second order rate constants, $k_f$ for hemiketal formation from dimethyl acetylphosphonate with various alcohols, as well as the reverse reaction rate constants, $k_r$ to starting materials, were determined. The kinetic isotope effect of 2.8 for the forward reaction $k_f$ (EtOH addition) and the backward reaction $k_r$ indicates a general catalysis pathway. On the other hand, the calculated values of the enthalpies of activation $\Delta H^‡ = 10.37$ kcal mol$^{-1}$ (forward), $\Delta H^‡ = 13.66$ kcal mol$^{-1}$ (backward) and the entropies of activation, $\Delta S^‡ = -17.25$ cal mol$^{-1}$ K$^{-1}$ (forward), $\Delta S^‡ = -9.82$ cal mol$^{-1}$ K$^{-1}$ (backward) are not in accord with high molecularity of the reaction (1 cal = 4.184 J). Our analysis led to the conclusion that this is probably due to the fact that the transition state is mainly reactant-like with the development of only limited extent of bond formation. Various plausible reaction pathways for hemiketal formation are discussed. In addition, we have calculated the value of 2.65 $\sigma^*$ for the P(O)(OMe)$_2$ group based on proton affinity obtained from heats of formation ($\Delta H_f$) of applying the MNDO techniques. The following linear correlation between p*K*a values and PA values of hemiketals of the form (Me)(R)C(OH)(OCH$_2$X) was developed: $pK_a = PA - 356.58 + 9.18[\sigma^*(Me) + \sigma^*(R) + 0.2\sigma^*(X)]$.**

## Introduction

Acylphosphonates (α-ketophosphonates) are versatile compounds and their derivatives have lately received increasing attention.[1] Our laboratory has been involved in the study of the chemistry of acylphosphonic acids[2] and of oximes derived from them,[3] and in exploring acylphosphonic derivatives for the design of biologically active molecules. We have shown that the acylphosphonic function has the capability to interact with calcium *in vivo*, and thus to affect metabolic processes such as bone resorption and tissue calcification.[4] Acylphosphonates possess highly reactive carbonyl groups, capable of adding nucleophiles such as water, alcohols or amines to form hydrates or hemiketals, which may be followed by C–P bond cleavage to form carboxylic acids, esters or amides. Due to this unusual lability of their P–C bond, α-oxophosphonates have been subjected to a number of studies.[5] Dialkyl acylphosphonates hydrolyse in neutral solution in a two-step reaction which involves initial hydration of the carbonyl group, followed by P–C bond cleavage to give a dialkyl phosphite and carboxylic acid (Scheme 1).



**Scheme 1**

Under slightly acidic or neutral conditions the carbonyl hydration equilibrium is achieved rapidly, and the C–P bond cleavage ($k_2$) is rate determining.

The pathway delineated in Scheme 1 is reminiscent of that of trihalomethyl alkyl ketones[6] and of the haloform reaction[7] which share dualistic, ketone-like or carboxy-like behaviour with acylphosphonates. Both classes form oximes (or oxime ethers) when treated with (*O*-alkyl)hydroxylamine(s) (ketone-like).[8] Also in both cases, stable carbonyl hydrates or hemiketals are obtained in neutral or acidic water or alcohol solutions (ketone-like). In both cases (P–C or C–C) bond cleavage takes place from the tetrahedral addition intermediate under basic conditions (carboxy-like).[9–15] The driving force for this bond cleavage probably arises from the strong electron-withdrawing ability of the two groups, CX$_3$ and O=P(OR)$_2$, which bestow high electrophilicity on the carbonyl groups toward nucleophiles, and on the other hand, are capable of serving as relatively good leaving groups.

On the other hand, electron deficient carbonyl groups capable of yielding stable hydrates are of recent interest as 'transition state' (TS) analogues.[16] Acylphosphonates have not yet been used for the design of TS analogues. Consequently, it is of interest to study the effect of structural factors on carbonyl-hydrate–hemiketal equilibria. Since the $^{31}P$ chemical shift of the phosphorus atom is highly sensitive to the state of hybridization of its carbon neighbour (acylphosphonates appear at *ca.* 0 ppm, while their respective hemiketals appear around 17–21 ppm in the $^{31}P$ NMR spectrum), $^{31}P$ NMR spectroscopy is a uniquely convenient tool for the study of such equilibria. In this paper we report the results of our studies on the effect of the structure of alcohol on the hemiketal formation of two representative acylphosphonate

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esters, and proton affinity calculations on some selected hemiketals containing strongly electron-withdrawing (including dimethylphosphonyl) groups.

## Experimental

### Materials and instruments

Dimethyl acetylphosphonate, **1**, and dimethyl benzoylphosphonate, **2**, were synthesized as previously described.[2] The alcohols employed in this work are available commercially and were distilled prior to use. NMR spectra were recorded on a Varian VXR-300S instrument. The spectra were referenced to $SiMe_4$ as internal standard ($^1H$) and to 85% $H_3PO_4$ as external standard ($^{31}P$). Positive chemical shifts are downfield from the reference. $^{31}P$ spectra were $^1H$ decoupled. All spectra were performed using repetition time sufficiently long for complete relaxation. Broad band $^1H$ decoupling did not affect $^{31}P$ signal integration, as confirmed by comparing the integration of decoupled to that of coupled signals.

$RC(:O)P(:O)(OMe)_2$

**1** R = Me
**2** R = Ph

### Kinetics

Compound **1** or **2** (2 mmol) was dissolved in the appropriate alcohol (2–4 ml) and the solution was examined by $^{31}P$ NMR spectroscopy at 18 °C, monitoring the changes in the relative intensities of the phosphonate ($\delta = -1.77$ and 0.1 for **1** and **2**, respectively) and the hemiketal signals ($\delta = 17.6$–21). In several cases the formation of some dimethyl phosphite derived from the hemiketals was also observed ($\delta$ *ca.* 12.4, $J = 700$ Hz).

### Proton affinity calculations

The gas-phase proton affinity (PA) of the base $\mathbf{A}^-$ (hemiketal anion of **1** or **2**) is defined[17] as standard enthalpy change of the reaction in gas phase, represented in eqn. (1).

$$\mathbf{A}^- + H^+ \longrightarrow \mathbf{A}H \qquad (1)$$

PA values were calculated according to eqn. (2) in which $\Delta H_f$

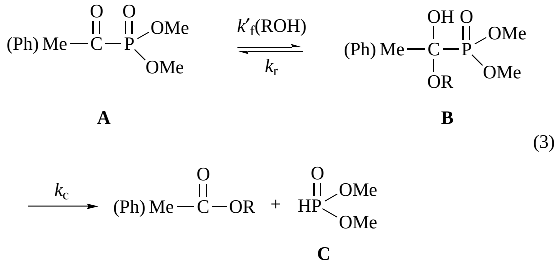
$$(PA) = -\Delta H = +\,|\Delta H_f(\mathbf{A}H)| - \Delta H_f(\mathbf{A}^-)| + \Delta H_f(H^+) \qquad (2)$$

is the enthalpy of formation of the various species in the gas-phase at 298 K. $\Delta H_f$ of $H^+$ has been taken as 365.7 kcal $mol^{-1}$.[18] Heats of formation ($\Delta H_f$) were computed by semiempirical SCF calculations applying the MNDO[19] techniques corrected to the MNDO/H version.[20] Total geometry optimization including internal rotation was performed for each of the molecular species. Second derivatives were estimated for all $3N - 6$ geometrical parameters during optimization. The minima were verified through the second derivatives (Hessian) matrix eigenvalues which must be all positive. DEP[21] analytical gradients were used throughout the optimization. Entropies were calculated by evaluation of the vibrational rotational and translational partition functions.

## Results

### Kinetics

The kinetic scheme ascribed to hemiketal formation (to reach equilibrium) from **1** or **2**, followed by a decomposition step to yield dimethyl phosphite and alkyl carboxylate, is depicted in eqn. (3).


(3)

In this equation $k'_f = k_f[ROH]$ and the equilibrium constant $K'_f = K_f[ROH] = k'_f/k_r$. In almost all the cases the approach to equilibrium $K'_f$ is fast as compared to the decomposition step $k_c$ and the equilibrium is achieved when only a few percent of dimethyl phosphite (**C**) is formed. The rate constants $k'_f$, $k_r$ and $k_c$ were determined by fitting the data to at least one of the following three kinetic expressions, eqns. (4), (5) and (6). $A_0$, $A_t$ and $A_e$ are the integrated $^{31}P$ NMR signals of the phosphonate (**A**) at $t = 0$, time $t$ and at equilibrium, respectively. Since $B_e/A_e = K'_f = k'_f/k_r$, the values of the forward ($k'_f$) and the reverse ($k_r$) rate constants can be derived.

$$\ln (A_0 - A_e)/(A_t - A_e) = (k'_f + k_r)\,t = k_{obs}t \qquad (4)$$

$$A_t/A_0 = \exp\,[-(k'_f + k_r)t + k_r/(k'_f + k_r)] \qquad (5)$$

$$dA/dt = k_r[\mathbf{B}] - k'_f[\mathbf{A}];\ dB/dt = k'_f[\mathbf{A}] - k_r[\mathbf{B}];\ dC/dt = k_r[\mathbf{B}] \qquad (6)$$

Eqn. (5) delineates the kinetic rate expression of a first-order process approaching equilibrium. The time–concentration data were fitted to eqn. (5) by means of non-linear least-squares regression using the program PCNONLIN version 4 (SCI software). This program can also deal with fitting the observed data such as the disappearance of **A** *vs.* $t$ or the appearance of **B** or **C** *vs.* $t$, or the combined data of **A** + **B**, **A** + **C**, **B** + **C** and **A** + **B** + **C** *vs.* $t$, to the simultaneous differential kinetic eqn. (6) derived from eqn. (3).

Most of our results emerged from eqn. (6) employing at least two sets of coupled data. The equilibrium constants $K'_f$, $K_f = k_f/k_r$, together with the rate constants $k'_f$, $k_f$, $k_r$ and some values of $k_c$ are summarized in Table 1.

To check whether there are any enolic species present in the acylphosphonate solutions, we have examined the $^1H$ NMR spectrum of compound **1** in $CDCl_3$ and $CD_3OD$. No peaks corresponding to vinylic protons expected for the enol form $CH_2{=}C(OH)(PO_3Me)_2$ were observed. The $^1H$ NMR spectrum in $CDCl_3$ showed only the presence of two doublets at $\delta$ 2.49 (d, $J_{PCH}$ 5.3) and at $\delta$ 3.88 (d, $J_{POH}$ 10.7), due to the $CH_3CO$ and the $P{-}O{-}CH_3$ groups, respectively. In $CD_3OD$ four doublets were observed: two corresponding to the ketone [(**A**) $\delta$ 2.45 (d, $J_{PCH}$ 5.5) $CH_3CO$ and $\delta$ 3.86 (d, $J_{POH}$ 11.0), $P(OMe)_2$] and two to the hemiketal [(**B**), $\delta$ 1.47 (d, $J_{PH}$ 12.5) $CH_3C(OD)(OCD_3)$ and $\delta$ 3.80 (d, $J_{PH}$ 10.5) $P(OCH_3)_2$].

### Proton affinity

In order to evaluate the electron-withdrawing ability of the dimethoxyphosphinyl group and its effect on the $pK_a$ of the phosphonohemiketals **B** formed from the various alcohols [see eqn. (3)] we have employed the theoretical approach based on proton affinity (PA) calculations. For this, the heat of formation ($\Delta H_f$) was calculated for the neutral hemiketals (**BN**) and the charged hemiketal anions (**BC**) depicted in eqn. (7). $\Delta H$(RN) and $\Delta H$(RC) refer to the heats of formation of **BN** and **BC** from their constituents [X−CO−Y + ROH ($RO^-$)], respectively. In addition, we have also calculated the **PA** values of hemiketals **D** [$CH_3CR(OH)(OMe)$]. These hemiketals are derived from the addition of ethanol to a series of ketones, in contrast to the previous examples (**BN a–g**) which were derived from the addition of a series of alcohols to a series

**Table 1** Equilibrium constants ($K'_f$, $K_f$),[a] pseudo-first-order ($k'_f$) and second-order rate constants ($k_f$)[a] for the formation of hemiketals from dimethyl acetylphosphonate **1** [Table 1(*a*)] and from dimethyl benzoylphosphonate **2**[b] [Table 1(*b*)] by various alcohols, $RCH_2OH$, at 18 °C, and first-order rate constants for the breakdown of the hemiketals to reactants ($k_r$) and to dimethyl phosphite ($k_c$)

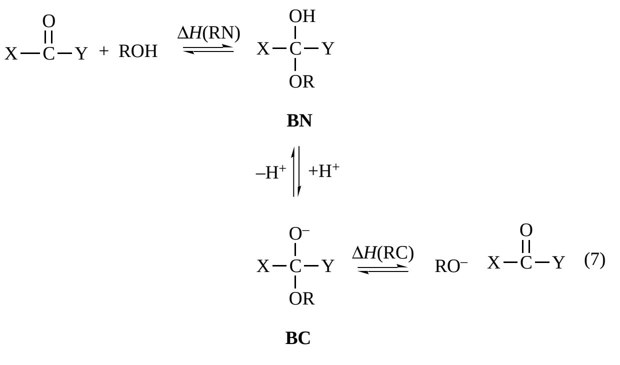
| R | $\sigma^*$ | p$K_a$ of $RCH_2OH$ | $K'_f$ | $K_f/10^{-2}$ $dm^3\ mol^{-1}$ | Be[c] (%) | $k'_f/10^{-2}$ $min^{-1}$ | $k_f/10^{-2}$ $dm^3\ mol^{-1}\ min^{-1}$ | $k_r/10^{-2}$ $min^{-1}$ | $k_c/10^{-2}$ $min^{-1}$ |
|---|---|---|---|---|---|---|---|---|---|
| (*a*) | | | | | | | | | |
| $CH_3(CH_2)_4$– | | | 2.50 | 31.30 | 71.6 | 10.10 | 1.260 | 4.00 | |
| $CH_3(CH_2)_2$– | | | 2.60 | 20.90 | 72.2 | 9.60 | 0.770 | 3.70 | |
| $CH_3CH_2$– | | | 3.17 | 23.60 | 76.0 | 9.20 | 0.686 | 2.90 | |
| $CH_3$– | 0.0 | 15.90 | 2.90 | 16.90 | 74.3 | 6.12 | 0.356 | 2.11 | 0.029 |
| $CH_3$– 40 °C | | | 1.95 | 11.30 | 66.1 | 23.00 | 1.340 | 11.80 | 0.160 |
| $CH_3$– (ROD) | | | 2.80 | 16.30 | 73.5 | 2.20 | 0.128 | 0.79 | |
| H– | 0.49 | 15.54 | 8.2 | 33.10 | 89.1 | 31.20 | 1.25 | 3.80 | 0.031 |
| $CH_3OCH_2$– | 0.52 | 14.82 | 1.77 | 14.00 | 64.0 | 1.60 | 0.126 | 0.90 | |
| $ClCH_2$– | 1.05 | 14.36 | 0.54 | 3.86 | 35.0 | 1.20 | 0.085 | 2.30 | 0.16 |
| CH≡C– | 1.65 | 13.55 | 0.36 | 2.12 | 26.0 | 1.20 | 0.073 | 3.39 | |
| $Cl_2CH$– | 1.94 | 12.89 | 0.12 | 0.97 | 11.4 | 0.10 | 0.0081 | 0.78 | |
| $CF_3$– | 2.50 | 12.24 | 0.07 | 0.49 | 6.8 | 0.03 | 0.0021 | 0.42 | |
| (*b*) | | | | | | | | | |
| H– | 0.49 | 15.54 | 1.06 | 4.26 | 51.4 | 0.38 | 0.015 | 0.361 | 0.026 |

[a] The molar concentrations of the alcohols were calculated from their densities and were assigned as follows: hexan-1-ol 7.98; butan-1-ol 12.43; propan-1-ol 13.4; ethanol 17.15; methanol 24.73; 2-methoxyethanol 12.69; 2-chloroethanol 14.1; prop-2-ynyl alcohol 16.93; 2,2-dichloroethanol 12.31; 2,2,2-trifluoroethanol 14.68 M. $K_f = K'_f/[ROH]$; $k_f = k'_f/[ROH]$. [b] Reaction with dimethyl benzoylphosphonate, **2**, was carried out only with methanol. [c] Be (%) specifies the percentage of hemiketal at equilibrium.

**Table 2** Calculated (MNDO) $\Delta H_f$, $\Delta H(R)$ and $\Delta G(R)$ values at 298 K of the neutral (**BN a**) and the negatively charged (**BC a**) formaldehyde hemiacetals [X = Y = H, eqn. (7)] formed by various alcohols, $RCH_2OH$, and their corresponding proton affinity (PA) values in kcal $mol^{-1}$

| | | Charge = 0 | | | Charge = −1 | | |
|---|---|---|---|---|---|---|---|
| R | $\sigma^*$ | $-\Delta H_f$ | $-\Delta H$(RN) | $-\Delta G$(RN) | $-\Delta H_f$ | $-\Delta H$(RC) | PA/ kcal $mol^{-1}$ |
| $CH_3$– | −0.1[a] | 106.553 | 56.963 | 45.21 | 97.777 | 65.844 | 374.48 |
| H– | 0.0[a] | 101.231 | 57.626 | 45.64 | 92.611 | 66.234 | 374.32 |
| $Cl(CH_2)_2$– | 0.39 | 119.917 | 57.440 | 45.30 | 112.707 | 63.490 | 372.91 |
| $CH_3OCH_2$– | 0.52 | 143.641 | 54.816 | 43.19 | 136.561 | 64.190 | 372.78 |
| $ClCH_2$– | 1.05 | 114.490 | 57.125 | 45.36 | 110.230 | 59.243 | 369.96 |
| $FCH_2$– | 1.10 | 150.026 | 57.131 | 45.49 | 145.276 | 58.151 | 370.45 |
| $Cl_2CH$– | 1.94 | 116.692 | 57.277 | 45.46 | 116.362 | 53.846 | 366.03 |
| $F_2CH$– | 2.05 | 198.338 | 57.399 | 44.14 | 197.678 | 55.321 | 366.36 |
| $CF_3$– | 2.50 | 250.826 | 57.535 | 45.49 | 253.046 | 50.750 | 363.48 |
| $CCl_3$– | 2.65 | 115.200 | 57.252 | 45.21 | 119.200 | 48.343 | 361.70 |

[a] These $\sigma^*$ values fit well the correlations displayed in Figs. 1 and 2 [also eqns. (8), (9) and (10)].



**a** X = Y = H; **b** X = H, Y = $CH_3$; **c** X = $CH_3$, Y = $CH_3$; **d** X = $CH_3$, Y = $CH_2Cl$; **e** X = $CH_3$, Y = $CHCl_2$; **f** X = $CH_3$, $CCl_3$; **g** X = $CH_3$, Y = $PO(OMe)_2$

of carbonyl compounds. The results are summarized in Tables 2 and 3.

Proton affinity values of the above described hemiacetals **BN a–g** (Tables 2 and 3) were plotted *vs.* the electron-withdrawing constants of the alkyl groups R in Fig. 1. Similarly, the proton affinities of the hemiketals **D** [$CH_3CR(OMe)(OH)$] *vs.* the Taft $\sigma^*$ constants of the residues R are plotted in Fig. 2. In all the cases tested (Figs. 1 and 2) linear correlations between PA and σ* were found.

## Discussion

### The inductive effect of the dimethoxyphosphinyl group

Tetrahedral intermediates have been shown to be formed in a variety of carbonyl reactions[22] either as transient or as stable species. Recently, due to their biochemical significance, reactions at carbonyl centres linked to phosphate or phosphonate esters have attracted considerable attention. The formation of relatively stable hemiketals, detectable by $^{31}P$ NMR, in alcohol solutions of acylphosphonates implies that the dimethoxyphosphinyl group is strongly electron withdrawing. Several attempts have been made to evaluate the substituent constant ($\sigma^*$) of the diethoxyphosphinyl [$-P(O)(OC_2H_5)_2$] group. Martin and Griffin[23] determined a value of $\sigma^* = 0.78$ for dimethoxyphosphinylmethyl group [$-CH_2P(O)(OMe)_2$] and by employing a fall-off factor of 2.8 due to the interposition of the methylene group, an approximate value of $\sigma^* = 2.18$ was obtained. This value is intermediate between the polar substituent constants ascribed to $F_2CH$ ($\sigma^* = 2.05$) and $F_3C$ ($\sigma^* = 2.50$) groups.[24]

In other work which was done by plotting the $^{17}O$ NMR chemical shifts of the carbonyl oxygens of two series of ketones *p*-$YC_6H_4COPO(OR)_2$ and *p*-$YC_6H_4COCF_3$, *vs.* $\sigma^*$ values of substituents Y the $\rho^+$ values of 29.0 and 27.4 were obtained for the trifluoromethyl and dimethoxyphosphinyl groups, respectively.[25] From these $\rho^+$ values the $\sigma^*$ value of the dimethoxy-

**Table 3** Calculated proton affinity values [(PA) kcal $mol^{-1}$] of acetaldehyde hemiacetal (**BN b**), hemiketals (**BN c**,**d**,**e**,**f**), hemiketals (**D**) and phosphonoketals [**BN g**]

| R | σ* | Hemiacetal **BN b** | Hemiketal **BN c** | Hemiketal **BN d** | Hemiketal **BN e** | Hemiketal **BN f** | Phosphonate **1** **BN g** | Hemiketal **D** |
|---|---|---|---|---|---|---|---|---|
| $CH_3$– | −0.1[a] | 372.96 | 372.82 | 362.49 | 352.58 | 343.84 | 345.31 | |
| H– | 0.0[a] | 372.89 | 372.36 | 361.62 | 352.50 | 343.72 | 344.89 | 372.28 |
| $Cl(CH_2)_2$– | 0.39 | 368.70 | 370.97 | 360.53 | 351.07 | 342.43 | 343.74 | 368.39 |
| $CH_3OCH_2$– | 0.52 | 369.95 | 370.01 | 360.00 | 350.61 | 341.59 | 343.36 | 368.06 |
| $ClCH_2$– | 1.05 | 367.58 | 367.61 | 357.88 | 348.72 | 340.53 | 341.80 | 362.49 |
| $FCH_2$– | 1.10 | 367.35 | 367.30 | 357.68 | — | 340.30 | 341.65 | 364.02 |
| $Cl_2CH$– | 1.94 | 364.87 | 363.60 | 354.32 | 346.25 | 338.61 | 338.71 | 352.58 |
| $F_2CH$– | 2.05 | 365.28 | 363.11 | 353.88 | 345.28 | 337.89 | 338.87 | 354.49 |
| $CF_3$– | 2.50 | 361.20 | 361.08 | 352.08 | 343.71 | 336.35 | 337.54 | 346.27 |
| $CCl_3$– | 2.65 | 360.74 | 360.40 | 351.48 | 342.77 | 335.36 | 337.45 | 343.83 |

[a] These σ* values fit well the correlations displayed in Figs. 1 and 2 [also eqns. (8), (9) and (10)].

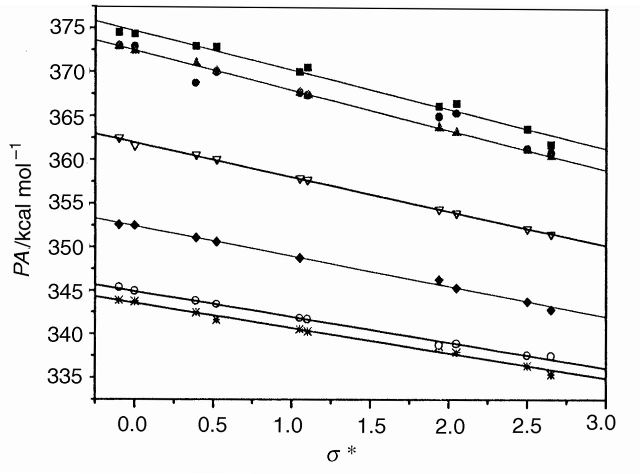


**Fig. 1** Proton affinities (PA) of hemiacetals, hemiketals and phosphonohemiketals *vs.* σ*. **BN a** -■-; **BN b** -▲-; **BN c** -●-; **BN d** -▽-; **BN e** -◆-; **BN f** -*-; **BN g** -O- (acylphosphonate).

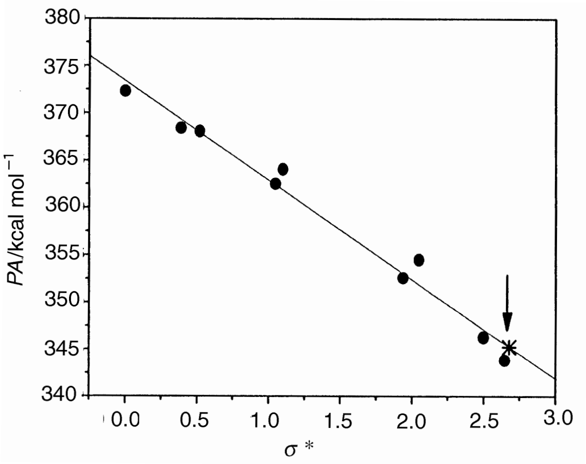


**Fig. 2** Proton affinities (PA) of hemiketals (**D**) [$CH_3$–C(OH)(OMe)–R] *vs.* σ*. The * is assigned to R = $P(O)(OMe)_2$. σ* = 2.66.

phosphinyl group can be deduced by the following calculation: 2.6 × 27.4/29, which gives the result σ* = 2.45.

In an attempt to separate between the inductive ($\sigma_I$) and the mesomeric effects ($\sigma_R$) of phenylphosphonyl derivatives (Ph–POXY) a linear correlation between *meta*- and *para*-carbon chemical shifts and the Taft constants $\sigma_I$ and $\sigma_R$ was performed. The constants $\sigma_I$ and $\sigma_R$ thus derived for the dimethoxyphosphinyl group were +0.30 and +0.16, respectively.[26] This means that the dimethoxyphosphinyl group possesses high electron-withdrawing ability. The inductive and the mesomeric effects of dimethoxyphosphinyl group are comparable to those of the trifluoromethyl ($\sigma_I$ = +0.41) and nitro ($\sigma_R$ = +0.16) groups.[27]

Our approach to evaluate the electron-withdrawing parameters of $-PO(OR)_2$ group is based on the apparent linear relationship between the calculated proton affinity values and the substituents constants (σ*) of a diversity of hemiacetals (**BN a** and **b**), hemiketals (**BN c–f** and **D**) and the phosphonoketal (**BN g**) derived from compound **1** (see Tables 2 and 3 and Figs. 1 and 2).

The close correlation (see Fig. 1) between the PA *vs.* σ* lines of phosphonohemiketal (**BN g**, –O–) and trichloroacetone hemiketal (**BN f**,–*–) indicates that the σ* values of these two groups are similar (σ* = 2.65). The corresponding lines are in accord with eqns. (8) and (9).

$$\text{PA (–o–)} = 344.89 - 2.939\sigma^* \qquad (8)$$

$$\text{PA (–*–)} = 343.55 - 2.881\sigma^* \qquad (9)$$

The PA values of hemiketals [$CH_3C(OH)(OMe)$–R] derived from the addition of ethanol to α-substituted acetone *vs.* σ* values are displayed in Fig. 2. From this figure the value of σ* for R = $-PO(OMe)_2$ was found to be 2.66 (see arrow in the lower right corner of Fig. 2). The line in Fig. 2 obeys eqn. (10).

$$\text{PA} = 373.58 - 10.60\sigma^* \qquad (10)$$

In addition to the above correlations, our further concern was to define an appropriate relationship between the proton affinity values and the ionization constants of hemiketals.

Proton ionization constants of hemiacetals and hemiketals $R^1R^2C(OH)(OCH_2X)$ as a function of the polar effects of substituents $R^1$, $R^2$, $OCH_2X$, are consistent with eqn. (11).

$$pK_a = 14.19 - 1.315[\sigma^*(R^1) + \sigma^*(R^2)] + 0.3 - 0.2[pK_a(EtOH) - pK_a(HOCH_2X)] \qquad (11)$$

In eqn. (11) the increment of 0.3 was introduced to correct for replacing OH by OMe in the correlation of Hine and Koser[28] in which the $pK_a$ values of hemiketals $R^1R^2C(OH)_2$ are $pK_a = 14.19 - 1.315[\sigma^*(R^1) + \sigma^*(R^2)]$.

Since a fall-off factor of $0.2^5$ is assigned to substituents (X) in hemiketals $R^1R^2C(OH)(OCH_2X)$ [or hemiacetals, ($R^1$ = H; $R^1 = R^2$ = H)] a very good correlation between $pK_a$ and σ* values is attained by eqn. (12), where σ*(X) is the σ* value of X

$$pK_a = 14.49 - 1.37[\sigma^*(R^1) + \sigma^*(R^2) + 0.2\sigma^*(X)]^* \qquad (12)$$

in $XCH_2OH$ (the corresponding σ* values of H and $CH_3$ were taken as 0 and −0.1). Regarding $R^1$ and $R^2$, σ* values of H and $CH_3$ in these positions are 0.49 and 0, respectively. In the case where $R^1 = R^2$ = H, the $pK_a$ value predicted by eqn. (12) has to be raised by 0.3. Eqn. (12) is valid also when $CH_2X$ is replaced by H, using $\sigma^*(\mathrm{H}) = 0.49$.

Eqn. (13) gives a satisfactory linear correlation between the

$$\mathrm{PA} = 371.07 - 10.55[\sigma^*(\mathrm{CH_3}) + \sigma^*(\mathrm{R}^2) + 0.2\sigma^*(\mathrm{X})] \quad (13)$$

proton affinities of hemiketals and $\sigma^*$ for $\mathrm{R}^1 = \mathrm{CH_3}$ and $\mathrm{R}^2 \neq \mathrm{H}$.

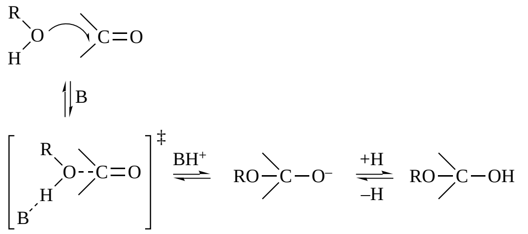
The combination of eqns. (12) and (13) gives eqn. (14) which

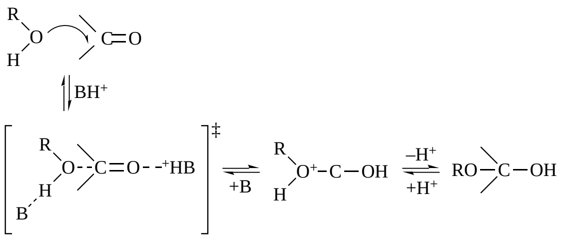
$$\mathrm{p}K_\mathbf{a} = \mathrm{PA} - 356.58 + 9.18\,[\sigma^*(\mathrm{CH_3}) + \sigma^*(\mathrm{R}^2) + 0.2\sigma^*(\mathrm{X})] \quad (14)$$

expresses the relationship between $\mathrm{p}K_\mathbf{a}$ and proton affinity values of hemiketals.

## Kinetics

The addition of water and alcohols to aldehydes has long been recognized to proceed *via* either class *n* general-base catalysis [eqn. (15)] in the addition direction, and the kinetically equivalent general-acid catalysis of the hemiacetal anion cleavage in the reverse reaction, or class *e* general acid catalysis [eqn. (16)][29,30] in the forward direction and general-base catalysis of proton removal from the cationic addition intermediate in the reverse reaction.


(15)

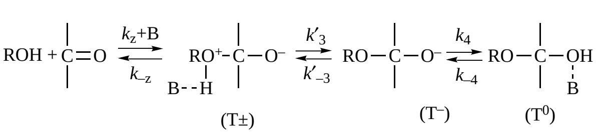

(16)

An indication of proton transfer in the rate-determining step of phosphono hemiketal formation or breakdown can be obtained from the solvent isotope effect for the reaction rates in $CH_3CH_2OH$ and $CH_3CH_2OD$. Indeed, Table 1 reveals that the deuterium isotope effect for the forward (hemiketal formation) and the backward (hemiketal breakdown to reactants) reactions is: $k_{\mathbf{f(CH_3CH_2OH)}}/k_{\mathbf{f(CH_3CH_2OD)}} = 2.8$, while $k_{\mathbf{r(CH_3CH_2OH)}}/k_{\mathbf{r(CH_3CH_2OD)}} = 2.7$, respectively. This observed ratio is in good agreement with the previously reported value of *ca.* 3 for the ratio of acetaldehyde ethylhemiacetal breakdown rate constants in water and deuterium oxide.[31] In the case of hemi-*ortho*-esters a higher value of 4.5 was found for the ratio breakdown rate constants of 2-hydroxy-2-phenyl-1,3-dioxolane.[32] Furthermore, the rate of alkoxide expulsion from the tetrahedral intermediate (without catalysis) is expected to increase with decreasing basicity of the leaving group. However, in the case of acylphosphonate hemiketals the rate constants in the backward direction ($k_r$) remain almost constant for a wide range of alkoxide basicity and slightly decrease (surprisingly) with the decrease in the basicity of two of the leaving groups ($CF_3CH_2OH$ and $Cl_2CHCH_2OH$, see Table 1).

Eqns. (15) and (16) outline reaction pathways in which proton transfer and carbon–oxygen bond formation proceed in a concerted manner. This can be the case only if the lifetime of the zwitterionic intermediate $\mathbf{T}^\pm$ (Table 4) is so short that it does not exist as a discrete intermediate. This requires that the reverse reaction of the zwitterion $\mathbf{T}^\pm$ to reactants (ROH + acylphosphonate) should be very rapid and in the range of diffusion controlled processes. Catalysis *via* a stepwise mechanism may occur if the backward reaction of $\mathbf{T}^\pm$ is faster than the proton switch to give the neutral product $\mathbf{T}^0$. The rate determining step can then be the trapping of the zwitterionic intermediate by the solvent (alcohol) to mediate a proton switch to form $\mathbf{T}^0$.

Constants of protonic equilibria of the various tetrahedral intermediate species are displayed in Table 4.

In a stepwise mechanism [eqn. (17)] where $K_\mathbf{ad} = K_\mathbf{f} = k_\mathbf{f}/k_\mathbf{r}$


$$\mathrm{ROH} + \mathrm{C{=}O} \underset{k_{-z}}{\overset{k_z+\mathrm{B}}{\rightleftharpoons}} \underset{(\mathrm{T}\pm)}{\mathrm{RO^{+}(H{\cdots}B){-}C{-}O^{-}}} \underset{k'_{-3}}{\overset{k'_3}{\rightleftharpoons}} \underset{(\mathrm{T}^-)}{\mathrm{RO{-}C{-}O^{-}}} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \underset{(\mathrm{T}^0)}{\mathrm{RO{-}C{-}OH{\cdots}B}} \quad (17)$$

and B = ROH (solvent), the rate constant of proton transfer from $\mathbf{T}^\pm$ to the solvent (B) can be evaluated by the expression $k'_\mathbf{3} = k_\mathbf{obs}K_\mathrm{s}/K_\mathbf{ad}$; $k_\mathbf{obs} = k_\mathbf{f}$; $K_\mathbf{s} = \mathbf{T}^0/\mathbf{T}^\pm$.

The various alcohols exhibited rate constants in the order of $k'_\mathbf{3} = 10^7$–$10^8$ $\mathrm{s}^{-1}$, which are smaller than the diffusion-controlled rate. This is probably due to the fact that intermediate $\mathbf{T}^\pm$ is a somewhat stronger base than the ROH solvents (see Table 4). The equilibrium constants for $\mathbf{T}^\pm$ formation from starting materials were calculated from the equation $K_\mathbf{z} = K_\mathbf{ad}/K_\mathbf{s}$ and values obtained are in the order of $1.85 \times 10^{-12}$ $\mathrm{dm}^3$ $\mathrm{mol}^{-1}$ (ethanol) and $1.09 \times 10^{-15}$ $\mathrm{dm}^3$ $\mathrm{mol}^{-1}$ (trifluoroethanol). Based on $k_{-z}$ *ca.* $10^{-11}$, the magnitudes of the corresponding $k_\mathbf{z}$ rate constants for the formation of $\mathbf{T}^\pm$ were estimated to be 0.185 and $1.09 \times 10^{-4}$ $\mathrm{dm}^3$ $\mathrm{mol}^{-1}$ $\mathrm{s}^{-1}$.

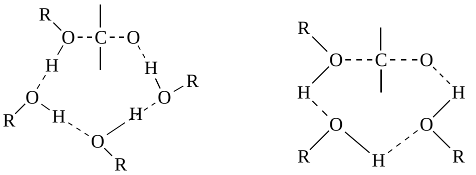
For weak bases the diffusional separation of $\mathbf{B}\mathrm{H}^+$ from $\mathbf{T}^-$ ($k_\mathbf{b}$) is expected to be the rate-limiting step in the forward direction.[33] However, since the proton transfer occurs before the rate-limiting step the equilibrium isotope effect will appear in the observed rate constant.

In the reverse direction, the rate-limiting step for the hemiketal breakdown is proton transfer from $\mathbf{T}^-$ to $\mathbf{T}^\pm$ (step $k_{-3}$). The rate constants were calculated by eqn. (18). This

$$k_\mathbf{obs}\,(k_{-1}) = k'_{-3}K_\mathbf{4}/K_\mathbf{BH} = k'_\mathbf{3}\,K_\mathbf{4}/K_\mathbf{3},(k'_{-3}/k'_\mathbf{3} = K_\mathbf{BH}/K_\mathbf{3}) \quad (18)$$

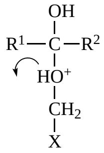
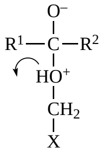
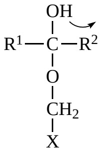
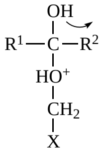
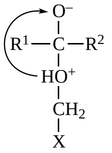
equation provides values of $k'_\mathbf{3} = 3.2 \times 10^7$, $k'_{-3} = 3.8 \times 10^8$ $\mathrm{s}^{-1}$ for ethanol, and $k'_\mathbf{3} = 3.12 \times 10^8$ $k'_{-3} = 1.75 \times 10^9$ $\mathrm{s}^{-1}$ for 2,2,2-trifluoroethanol. This stepwise process requires that $\mathbf{T}^-$ will have sufficient lifetime to be trapped by the solvent-mediated proton transfer to give $\mathbf{T}^\pm$ intermediate.

In terms of Jencks' libido rule,[34] it seems that there is little driving force for the concerted mechanism where the solvent (ROH) acts as general base. The product of addition of alcohol to the carbonyl group ($\mathbf{T}^\pm$) is a weaker acid than the conjugate acid of the free alcohol (see Table 4); thus proton transfer from $\mathbf{T}^\pm$ to ROH will proceed through a thermodynamically unfavourable direction. However, since the catalyst ROH operates as a solvent, the transition state is probably highly solvated providing a bridging structure for proton transfer (Scheme 2).


**Scheme 2**

Hydrogen bonding in the solvated TS can elicit: (*a*) promotion of hydrogen transfer from the attacking nucleophile to the hydroxylic catalyst by increasing its basicity, (*b*) suppression of

**Table 4** p$K_a$ values of alcohols ($RCH_2OH$), protonated alcohols ($RCH_2OH_2^+$) and various protonated and non-protonated species of hemiacetals of the forms: $R^1CR^2(OH)(HO^+CH_2X)$, $R^1CR^2(^-O)(HO^+CH_2X)$, $R^1CR^2(OH)(OCH_2X)$ and $R^1CR^2(HO)(HO^+CH_2X)$, where $R^1 = CH_3$, $R^2 = P(O)(OCH_3)_2$ and X = R

| | | | |  |  |  |  |  |
|---|---|---|---|---|---|---|---|---|
| | | | | $T^+ \rightleftharpoons T^0$ | $T^\pm \rightleftharpoons T^-$ | $T^0 \rightleftharpoons T^-$ | $T^+ \rightleftharpoons T^\pm$ | $T^\pm \rightleftharpoons T^0$<br>$\log T^0/T^\pm$ |
| R | $\sigma^*$ | $RCH_2OH$ p$K_a$ | $RCH_2OH_2^+$ p$K_a$[a] | p$K_1$[b] | p$K_3$[c] | p$K_4$[d] | p$K_2$[e] | p$K_2$–p$K_1$ |
| $CH_3$– | 0.0 | 15.90 | −1.00 | −4.80 | −0.10 | 10.86 | 6.16 | 10.96 |
| H– | 0.49 | 15.54 | −1.44 | −5.25 | −0.55 | 10.73 | 6.03 | 11.28 |
| $CH_3OCH_2$– | 0.59 | 14.82 | −1.59 | −5.27 | −0.57 | 10.70 | 6.00 | 11.27 |
| $ClCH_2$– | 1.05 | 14.36 | −1.94 | −5.98 | −1.28 | 10.57 | 5.87 | 11.85 |
| CH≡C– | 1.65 | 13.55 | −2.47 | −6.36 | −1.66 | 10.40 | 5.70 | 12.06 |
| $Cl_2CH$– | 1.94 | 12.89 | −2.72 | −6.64 | −1.94 | 10.33 | 5.63 | 12.27 |
| $CF_3$– | 2.50 | 12.24 | −3.23 | −7.18 | −2.48 | 10.17 | 5.47 | 12.65 |

[a] p$K_a$ values were calculated from the equation p$K_a = -1.0 - 0.89\sigma^*$.[i] [b] The ionization constants (p$K_1$) were calculated from the following linear relationship: p$K_1 = -0.17 - 0.96\Sigma\sigma^*$. This equation was derived by employing the data cited in ref. 33(*a*) for the acid dissociation constants of protonated tetrahedral carbonyl hydrate adducts of the form: $R^1R^2C(OH)(OH_2^+)$, where $R^1$ = H, $CH_3$, $CF_3$ and $R^2$ = H, $CH_3$, $OCH_3$. The $\sigma^*$ values for OH and $OCH_3$ were defined as 2.15 and 2.15 − 0.49 = 1.66, respectively. Introduction of the value of $\sigma^* = 2.15$ for the OH to the equation: p$K_a = 17.03 - 1.32\Sigma\sigma^*$ [assigned in ref. 33(*a*) for $R^1R^2R^3COH$] resulted in good correlation between the predicted and the experimental p$K_a$ values (ref. 30). [c] p$K_3$ was derived by adding 4.7 to p$K_1$ (p$K_3$ = p$K_1$ + 4.7; see ref. 31). A similar conclusion was obtained by comparing the p$K_a$ values of methyl hydrogen acetylphosphonate (p$K_a$ = 0.5[ii]) and that of the monoanion of acetylphosphonic acid (p$K_a$ = 5.6,[34] or 5.2[iii]). The difference between the p$K_a$ values of the acid form and that of the monoanion is therefore in the range 4.7–5.1. [d] p$K_4$ was calculated according to eqn. (12). [e] p$K_2$ = p$K_1$ + p$K_4$ − p$K_3$.

[i] J. P. Guthrie, *J. Am. Chem. Soc.*, 1978, **100**, 5892; L. S. Levitt and B. W. Levitt, *Tetrahedron*, 1971, **27**, 3777. [ii] T. A. O'Brien, R. Kluger, D. C. Pike and R. B. Gennis, *Biochim. Biophys. Acta*, 1980, **10**, 613. [iii] H. B. F. Dixon, R. A. Giddens, R. A. Harrisson, C. E. Henderson, W. E. Norris, D. M. Parker, R. N. Perham, P. Slater and M. J. Sparkes, *J. Enzyme Inhibition*, 1991, **5**, 111.

the reverse reaction to reactants through a very rapid proton separation from the encountered complex *via* proton flow across the hydrogen bridges, and (*c*) proton transfer from the attacking nucleophile to the partial developing negative charge on the carbonyl group *via* a cyclic transition state involving a concerted synchronous proton donation and acceptance (Scheme 2). In the latter process the basicity of the alcohol oxygen and the acidity of the alcohol hydrogen are increased as the addition intermediate is generated along the reaction coordinate. This virtually generates thermodynamically favoured proton transfer as the reaction proceeds. In terms of a reaction coordinate diagram (see Fig. 4) a concerted trajectory will display a decreased energy barrier compared to the kinetic equivalent stepwise mechanism.[33a] This was also supported by theoretical calculations of carbonyl addition reactions.[35]

A concerted reaction mechanism involving one or several solvent molecules in the transition state would necessarily imply a substantial solvent isotope effect and entropic barrier. In fact, the data is not unequivocally in accord with this mechanism. A kinetic isotope effect of 2.8 found for the addition of ethanol to acylphosphonate ($k_f$) and for the reverse reaction to reactants ($k_r$), might account for general catalysis, but seems too small to be associated with several hydrogen bonds in the transition state.[36] On the other hand if proton transfer is not rate limiting in the transition state and takes place after the transition state is reached *via* a proton switch mechanism, with or without mediation by solvent, the isotope effect would be expected to be close to 1.

With respect to activation parameters, the values obtained are not compatible with high molecularity of the reaction. For the above mentioned forward reaction [$k_f$(EtOH)] the enthalpy and entropy of activation are: $\Delta H^\ddagger = 10.37$ kcal mol$^{-1}$, $\Delta S^\ddagger = -17.25$ cal mol$^{-1}$ K$^{-1}$. In the backward direction ($k_r$) the corresponding values are: $\Delta H^\ddagger = 13.66$ kcal mol$^{-1}$, and $\Delta S^\ddagger = -9.82$ cal mol$^{-1}$ K$^{-1}$. A concerted mechanism involving simultaneous proton transfer and nucleophilic attack through solvating molecules ($k_f$) or proton transfer to the departing leaving group ($k_r$) is generally characterized by large negative entropies of activation.[37] These relatively less negative $\Delta S^\ddagger$ values and the moderate solvent deuterium effect probably reflect the nature of the transition state along the reaction coordinates (Fig. 3). The diagram provides a way to characterize transition states in terms of structure–reactivity correlations and other experimental parameters. Compared to formaldehyde, acetaldehyde is less electrophilic and thus the reactants at the bottom of the diagram are more stabilized (lower energy) relative to the addition products at the top. The transition state will now be shifted uphill (higher energy) toward the upper right corner along or parallel to the reaction coordinate (Hammond effect) and downhill perpendicular to the reaction coordinate toward the lower right corner (anti Hammond effect). In the case of the dimethyl acylphosphonates the situation is quite different. Due to the strong electron-withdrawing ability of the dimethoxyphosphinyl group the carbonyl is more electrophilic and therefore, the bottom edge of the diagram is of higher energy compared to the upper corners. This directs the transition state to move toward the lower left corner of the diagram (position of higher energy) parallel to the reaction coordinate (Hammond effect) and toward a lower energy position perpendicular to the reaction coordinate. Consequently, the transition state of the acylphosphonate's reaction will resemble more the reactants with very small amount of bond formation and proton transfer. This representation conclusion can account for the observed activation parameters and the moderate solvent isotope effect. According to the above view, the transition state of the acylphosphonate's addition reaction is achieved through limited changes in the reactants. This implies that solvent reorganization, proton motion and charge development are very small compared to the ground state, and thus reflect less negative $\Delta S^\ddagger$ and relatively small $\Delta H^\ddagger$ values.

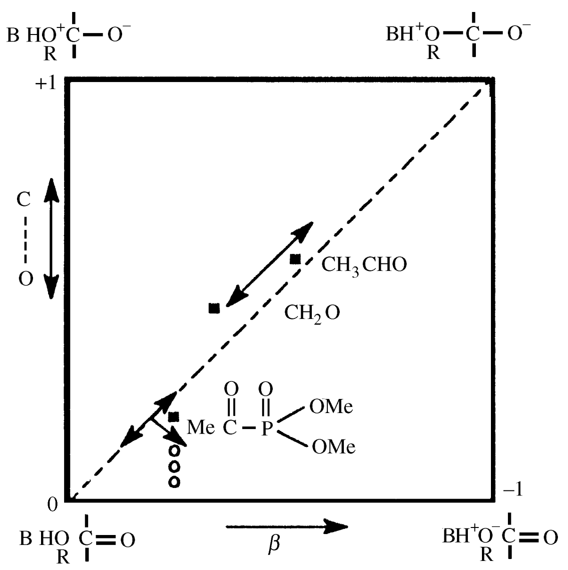


**Fig. 3** Reaction coordinate diagram for the solvent catalysed reaction for the addition of alcohols to dimethyl acetylphosphonate (class *n* mechanism). The horizontal and the vertical axes represent proton transfer and C–O bond formation/cleavage, respectively. The position of the transition state is changed along the diagonal line (Hammond effect) or in a perpendicular direction (anti-Hammond effect) depending on the nature of the perturbing factors.

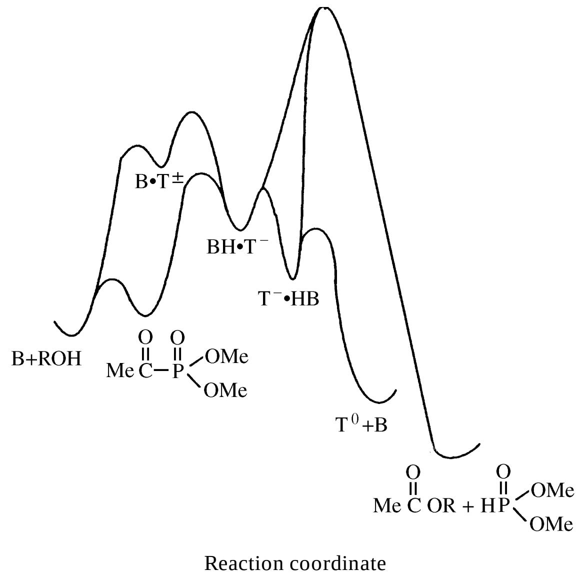


**Fig. 4** Reaction coordinate diagrams for rate-determining proton transfer in hemiketal formation ($k'_f$) and breakdown ($k_r$, $k_c$) during alcohol addition to acylphosphonates. The upper and the lower lines correspond to a stepwise and a concerted mechanism, respectively.

The fact that the isotope effect observed is not large may also suggest that only a limited amount of bond formation has developed between the attacking alcohol molecule and the carbonyl carbon atom. It should be stressed that the picture reached above is unexpected and not easy to accept since it was anticipated that a weak nucleophile such as ROH will form along the reaction coordinate a late transition state with significant bond and charge formation. This contradiction can be explained on the following basis. During the addition to the carbonyl bond to form $\mathbf{T}^{\pm}$ at least two parameters have to be taken into consideration,[10e] solvent interaction and C–O (charged) bond length. It has been shown that there is a remarkable effect on charge separation by changing the solution from water to methanol. The corresponding p$K_a$ values of 4-nitrophenol in water and methanol are 7.2 and 11.2.[38] This is also in accord with the normalized values of solvent polarity parameters $E^N{}_T$ which were determined to be 1.00, 0.790 and 0.654 for water, methanol and ethanol, respectively.[39] Thus, a corollary of this is that compared to water, ethanol (and methanol) restrain charge separation in the transition state and accordingly, a reactant-like transition state can be formed.

On the other hand, it is expected that alcoholysis of carboxylic esters containing strong electron-withdrawing substituents will exhibit similar thermodynamic parameters. However, this is not the case. For the neutral methanolysis of chloromethyl trichloroacetate, for pyridine-catalysed methanolysis of 4-nitrophenyl dichloroacetate and for neutral hydrolysis of 4-nitrophenyl trifluoroacetate, the entropies of activation are: −48.28,[40] −32.20[41] and −68.60[41] cal mol$^{-1}$ K$^{-1}$, respectively. These experimental data indicate either that the structural characteristics of the transition state of the $B_{AC}3$ mechanism proposed for the above mentioned di- and tri-haloacetate esters differ from that of the class *n* mechanism attributed to the alcohol addition to acylphosphonates, or that a mechanism involves the dissociation ($k_b$) of $\mathbf{BH}^+$ from $\mathbf{T}^-$ [eqn. (17)] formed within the encounter complex may also take place and should be considered as rate limiting step.

Relative to acetaldehyde the carbonyl group of benzaldehyde is stabilized by 2.7 kcal mol$^{-1}$.[10d] In the case of benzoylphosphonate (Table 1, compound **2**) the stabilization (reflected by $K_{ad}$) amounts only to 1.2 kcal mol$^{-1}$. However, regarding the addition reaction ($k_f$), the rate of addition of methanol to compound **2** is slower by a factor of 83 than that to compound **1**. This ratio is indeed consistent with an extra stabilization of 2.56 kcal mol$^{-1}$ (at 18 °C) conferred by the aromatic ring in **2** toward nucleophilic attack. Surprisingly, in the reverse reaction ($k_r$) the ratio of the rate constants is suppressed by a factor of eight implying that the addition product (hemiketal) is also stabilized but to a lesser extent (1.34 kcal mol$^{-1}$).

Although the reaction rate constants of the phosphite extrusion from the tetrahedral intermediates ($k_c$) have to be viewed with care, since they are derived only from the initial stage of the reaction, they nevertheless provide some interesting results. The partitioning ratios of the addition intermediate to reactants and products ($k_r/k_c$) are 73, 124 and 14 for ethanol, methanol and 2-chloroethanol, respectively (Table 1). Since the reverse reaction rates ($k_r$) of the above-mentioned intermediates are similar, it can be suggested that the alkoxy oxygen contributes to the departure of the phosphite group and probably donates a push to expel it from the tetrahedral intermediate. In such a case the more basic oxygens are more effective in promoting the extrusion of the leaving group.

It should be noted that in analogy to alcoholysis[6a] and aminolysis[6b] of trihalomethyl aryl ketones the departure of the phosphite group may proceed *via* either a stepwise E1cB type elimination process, where a fast pre-equilibrium proton transfer [$1/K_4$, eqn. (17)] precedes the rate-limiting step of $\mathbf{T}^-$ breakdown, or *via* a concerted E2 type mechanism, where $k_{-4}$ is rate determining. In a stepwise type mechanism the rate-limiting step in the reverse direction ($k_r$) is the formation of $\mathbf{T}^{\pm}$. Thus, along this path, the intermediates involved with the partitioning process, are $\mathbf{T}^-\mathbf{BH}$ and $\mathbf{BH}\cdot\mathbf{T}^-$ (Fig. 4). This implies that the push provided by the alkoxide oxygen to expel the phosphite is not disrupted by the proton transfer process, since the two processes take place independently. The same conclusion is reached also in the case of a concerted mechanism involving a simultaneous proton transfer from $\mathbf{T}^0$ by the solvent. The transition state of this reaction leads either to $\mathbf{B}\cdot\mathbf{T}^{\pm}$ or to $\mathbf{BH}\cdot\mathbf{T}^-$ which will then break down to reactants and phosphite. The activation parameters of phosphite expulsion: $\Delta H^{\ddagger} = 13.57$ kcal mol$^{-1}$, $\Delta S^{\ddagger} = -14.26$ cal mol$^{-1}$ K$^{-1}$, again do not support a multimolecular reaction.

### Equilibrium constants ($K_f$)

Several correlations have been proposed for hydration[10a,d,42,43] and the addition of methanol[44–46] to aldehydes and ketones. Kluger *et al.*[5b] had predicted that the equilibrium constant ($K'_f$) for the hydration of compound **1** is approximately 9. From eqn. (19)[45] and the data quoted in ref. 47 for the equilibrium

$$\log K'_f = 1.7\sigma^* - 2.81 \qquad (19)$$

constants ($K'_f$) of the formation of *gem*-diol derived from substituted acetone, the expected $K'_f$ value for $\sigma^* = 2.65$ is 49.5. This value is higher by a factor of 5.5 than the experimentally found value $K'_f = 9$. An equilibrium constant of 9 is consistent with a polar substituent value of $\sigma^* = 2.22$.

With regard to hemiketal formation, the equilibrium constant $K_f$ of methanol addition to acetylphosphonate **1** also seems to be smaller than the anticipated value deduced from the comparison with aliphatic ketones. The $K_f$ values cited in ref. 47 for hemiketal formation lead to the linear correlation displayed in eqn. (20). For $\sigma^* = 2.65$, the predicted value is 1.56 $dm^3 mol^{-1}$

$$\log K_f = 1.39\sigma^* - 3.49 \qquad (20)$$

which is again five times higher than the value of 0.33 $dm^3$ $mol^{-1}$ obtained experimentally (Table 1).

The equilibrium constants $K_f$ ($dm^3$ $mol^{-1}$) for the addition of various alcohols bearing electron-withdrawing substituents to dimethylacetylphosphonate, **1**, are summarized in Table 1. From the data presented it is possible to deduce the relationship between the substituent on the alcohol molecule on the equilibrium constants. On employing $\sigma^*$ values of 0 and 0.49 for $R = CH_3$ and H (in $RCH_2OH$), respectively, the corresponding $\rho^*$ and intercept values of $-0.725 \pm 0.1$ and $-0.515 \pm 0.14$ were obtained. A better correlation was reached when the respective $\sigma^*$ values for $R = CH_3$ and H were taken as $-0.1$ and 0 [eqn. (21)].

$$\log K_f = -0.674\,(\pm 0.057)\sigma^* - 0.63 \pm 0.08 \qquad (21)$$

The above correlation implies that the equilibrium constants and, concurrently the percentage (%Be) of the hemiketals formed, decline with the decreasing acidity of the attacking alcohols. However, this pattern of structure–reactivity relationship is inconsistent with the behaviour of methanol and ethanol. Due to its higher $\sigma^*$ and lower $pK_a$ value, methanol compared to ethanol is expected to display a smaller equilibrium constant, which is not the case. It seems that this effect is a general phenomenon since the inspection of the $K_f$ (methanol)/$K_f$ (ethanol) ratio in some other carbonyl compounds reveals that the corresponding values for formaldehyde, acetaldehyde, dichloroacetone and trifluoroacetophenone are: 1.43, 1.49, 1.84 and 3.32, namely it is consistently larger than unity.

## Conclusions

$^{31}P$ NMR spectroscopy made it possible to monitor the ketone–hemiketal equilibrium of two representative acylphosphonates with various alcohols, and allowed the determination of their equilibrium, and forward and backward rate constants.

From the heats of formation of a series of acylphosphonate (and other) hemiketals calculated by means of semiempirical quantum mechanical methodology (MNDO), their proton affinity values could be calculated. From the comparison of the proton affinity values of the acylphosphonate hemiketals with those of other ketones bearing electron-withdrawing substituents, the $\sigma^*$ of the dimethoxyphosphinyl group was found to be 2.66. This high $\sigma^*$ value reflects the similarity of the kinetic and thermodynamic behaviour of acylphosphonates to those of trihaloketones, both types having strongly electrophilic carbonyl groups.

We also calculated the protonic equilibria of all the intermediate species involved in the addition reactions leading to the hemiketal formation. The hemiketal formation takes place with a general base catalysis, class *n* type mechanism. Indeed, the kinetic isotope effect indicates the involvement of a proton transfer in the transition state. The not too negative $\Delta S$ value obtained for the acylphosphonate hemiketal formation is rationalized on the basis of the reaction coordinate diagram. Due to the strong electron-withdrawing effect of the dimethoxyphosphinyl group, the TS of the hemiketal-forming reaction resembles the reactants with only a limited amount of bond formation and breaking. Another possibility that may be in accord with such $\Delta S$ value is that the dissociation $BH^+$ from the $\mathbf{T}^-$ intermediate in the encounter complex is the rate-limiting step.

## References

1 Acylphosphonate reviews: Yu. A. Zhdanov, L. A. Uzlova and Z. I. Glebova, *Russ. Chem. Rev.* (*Engl. Transl.*), 1980, **94**, 843; E. Breuer, in *The chemistry of organophosphorus compounds*, ed. F. Hartley, Wiley, Chichester, 1996, vol. 4, pp. 653–729.

2 (*a*) E. Breuer, R. Karaman, H. Leader, A. Goldblum and R. Moshe, *Phosphorus and Sulfur*, 1987, **30**, 113; (*b*) E. Breuer, R. Karaman, H. Leader and A. Goldblum, *Phosphorus and Sulfur*, 1987, **33**, 61; (*c*) E. Breuer, R. Karaman, A. Goldblum and H. Leader, *J. Chem. Soc., Perkin Trans. 2*, 1988, 2029; (*d*) R. Karaman, A. Goldblum, E. Breuer and H. Leader, *J. Chem. Soc., Perkin Trans. 1*, 1989, 765.

3 (*a*) E. Breuer, R. Karaman, D. Gibson, H. Leader and A. Goldblum, *J. Chem. Soc., Chem. Commun.*, 1988, 504; (*b*) E. Breuer, R. Karaman, A. Goldblum, D. Gibson, H. Leader, B. V. L. Potter and J. H. Cummins, *J. Chem. Soc., Perkin Trans. 1*, 1988, 3047; (*c*) E. Breuer, R. Karaman, H. Leader and A. Goldblum, *J. Chem. Soc., Chem. Commun.*, 1987, 671; (*d*) J. Katzhendler, R. Karaman, D. Gibson, H. Leader and E. Breuer, *J. Chem. Soc., Perkin Trans. 2*, 1989, **2**, 589.

4 (*a*) G. Golomb, A. Schlossman, H. Saadeh, M. Levi, J. M. Van Gelder and E. Breuer, *Pharm. Res.*, 1992, **9**, 143; (*b*) G. Golomb, A. Schlossman, Y. Eitan, H. Saadeh, J. M. Van Gelder and E. Breuer, *J. Pharm. Sci.*, 1992, **81**, 1004; (*c*) E. Breuer, G. Golomb, A. Hoffman, A. Schlossman, J. M. van Gelder, H. Saadeh, M. Levi and Y. Eitan, *Phosphorus, Sulfur, and Silicon*, 1993, **76**, 167; (*d*) J. M. van Gelder, E. Breuer, A. Ornoy, A. Schlossman, N. Patlas and G. Golomb, *Bone*, 1995, **16**, 511.

5 (*a*) R. Kluger and J. Chin, *J. Am. Chem. Soc.*, 1978, **100**, 7382; (*b*) R. Kluger, D. Pike and J. Chin, *Can. J. Chem.*, 1978, **56**, 1972; (*c*) A. Narayanan and K. D. Berlin, *J. Am. Chem. Soc.*, 1979, **101**, 109; (*d*) K. D. Berlin and A. Taylor, *J. Am. Chem. Soc.*, 1964, **86**, 3862; (*e*) E. S. Krol, J. M. Davis and G. R. J. Tatcher, *J. Chem. Soc., Chem. Commun.*, 1991, 118.

6 (*a*) M. Uieara, C. Zucco, D. Zanette, M. C. Rezende and F. Nome, *J. Chem. Soc., Perkin Trans. 2*, 1987, 175; (*b*) J. Druzian, C. Zucco, M. C. Rezende and F. Nome, *J. Org. Chem.*, 1989, **59**, 4767; (*c*) C. Gustafson and M. Johanson, *Acta Chem. Scand.*, 1948, **2**, 42.

7 J. March, *Advanced organic chemistry*, McGraw-Hill, New York, 1977, 2nd edn., p. 575.

8 (*a*) K. D. Berlin, R. T. Claunch and E. T. Gaudy, *J. Org. Chem.*, 1968, **33**, 3090; (*b*) G. Holan, W. M. P. Johnson, K. Rihs and C. T. Virgona, *Pestic. Sci.*, 1984, **15**, 361.

9 There are many precedents which show that aldehydes and ketones bearing electron-withdrawing substituents strongly favour the hydrated (*gem*-diol) form.[10] Some of these are chloral,[11] fluoral[12] and trifluoroacetone hydrate.[13] This is also the case with transient tetrahedral intermediates formed from trifluoroacetic esters[14,22e] and amides.[15]

10 (*a*) R. P. Bell, *Adv. Phys. Chem.*, 1966, **4**, 1; (*b*) S. Patai, *The Chemistry of Carbonyl Group*, vol. II, Interscience, London, 1970, p. 1; (*c*) J. E. Meany and Y. Pocker, *J. Am. Chem. Soc.*, 1991, **113**, 6155; (*d*) P. Greenzaid, *J. Org. Chem.*, 1973, **18**, 3164; (*e*) R. P. Bell and P. E. Sorensen, *J. Chem. Soc., Perkin Trans. 2*, 1976, 1594.

11 M. M. Davies, *Trans. Faraday Soc.*, 1940, **86**, 1114.

12 H. Shechter and F. Courad, *J. Am. Chem. Soc.*, 1950, **72**, 3371.

13 A. L. Henne, M. S. Newman, L. L. Quill and R. A. Staniforth, *J. Am. Chem. Soc.*, 1947, **69**, 1819.

14 (*a*) F. Swarts, *Bull. Soc. Chim. Belg.*, 1929, **35**, 414; (*b*) M. L. Bender, *J. Am. Chem. Soc.*, 1953, **75**, 5986; (*c*) A. Moffat and H. Hunt, *J. Am. Chem. Soc.*, 1959, **81**, 2082; *J. Chem. Soc., Chem. Commun.*, 1977, 857.

15 (*a*) G. Fraenkel and D. Watson, *J. Am. Chem. Soc.*, 1976, **97**, 231; (*b*) A. Cipiciani, P. Linda and G. Savelli, *J. Chem. Soc., Chem. Commun.*, 1977, 857.
16 (*a*) R. Wolfenden, *Ann. Rev. Biophys. Bioeng.*, 1976, **5**, 271; (*b*) R. Wolfenden and L. Frick, *in Enzyme Mechanisms*, eds. M. I. Page and A. Williams, 1987, RSC, London, p. 97; (*c*) A. Tramontano, A. A. Amman and R. A. Lerner, *J. Am. Chem. Soc.*, 1988, **110**, 2282; (*d*) J. Jacobs, P. G. Schultz, R. Sugasawara and M. Powell, *J. Am. Chem. Soc.*, 1987, **109**, 2174; (*e*) A. P. Kaplan and P. A. Bartlett, *Biochemistry*, 1991, **30**, 8165.
17 D. H. Aue and M. T. Bowers, *Gas phase ion chemistry*, ed. M. T. Bowers, Academic Press, New York, 1979, vol. 2, ch. 9.
18 S. Olivella, F. Urpi and J. Vilarrassa, *J. Comput. Chem.*, 1984, **5**, 230.
19 M. J. S. Dewar and W. Thiel, *J. Am. Chem. Soc.*, 1977, **99**, 4899.
20 (*a*) A. Goldblum, *J. Comput. Chem.*, 1987, **8**, 835; (*b*) K. Ya. Burstein and A. N. Isaev, *Theor. Chim. Acta*, 1984, **64**, 397.
21 R. Fletcher, *Comput. J.*, 1970, **13**, 317.
22 (*a*) S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237; (*b*) W. P. Jencks, *Catalysis in chemistry and enzymology*, McGraw-Hill, New York, 1968, pp. 354–463; (*c*) T. C. Bruice and S. J. Benkovic, *Bioorganic mechanisms*, vol. 1, W. A. Benjamin, Inc., New York, 1966, pp. 1–211; (*d*) M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; see also *Mechanism of homogeneous catalysis from proton to proteins*, Wiley, New York, 1971, p. 108; (*e*) B. Capon, A. K. Ghosh and D. McL. A. Grieve, *Acc. Chem. Res.*, 1981, **14**, 306.
23 D. J. Martin and C. E. Griffin, *J. Org. Chem.*, 1965, **30**, 4034.
24 L. T. Kanerva and E. K. Euranto, *J. Chem. Soc.*, *Perkin Trans 2*, 1987, 441.
25 H. Dahn, P. Pechy and V. V. Toan, *Magn. Reson. Chem.*, 1990, **28**, 883.
26 H. Duddeck and R. Lecht, *Phosphorus and Sulfur*, 1987, **29**, 169.
27 T. Fujita and T. Nishioka, *Progress in physical organic chemistry*, ed. R. W. Taft, Wiley, New York, 1976, **12**, 49.
28 J. Hine and G. F. Koser, *J. Org. Chem.*, 1971, **36**, 1348.
29 L. H. Funderburk, L. Aldwin and W. P. Jencks, *J. Am. Chem. Soc.*, 1978, **98**, 5444.
30 (*a*) J. L. Palmer and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6472; (*b*) P. E. Sorensen and W. P. Jencks, *J. Am. Chem. Soc.*, 1987, **109**, 4675; (*c*) P. E. Sorensen, K. J. Pedersen, P. R. Pedersen, V. M. Kanagasabapapathy and R. A. McClelland, *J. Am. Chem. Soc.*, 1988, **110**, 5118.
31 C. A. Coleman and C. J. Murry, *J. Am. Chem. Soc.*, 1991, **113**, 1677.
32 B. Capon, M. I. Dosunmu and M. de N. de Matos Sanchez, *Adv. Phys. Org. Chem.*, 1985, **21**, 37.
33 (*a*) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, 1973, **95**, 5637; (*b*) H. Fischer, F. X. DeCandis, S. D. Ogden and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 1340.
34 J. P. Fox, M. I. Page, A. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1972, **94**, 4731.
35 I. H. Williams, *J. Am. Chem. Soc.*, 1987, **109**, 6299.
36 The solvent isotope effect for water reaction in ester hydrolysis was found to be in the range of $k(H_2O)/k(D_2O) = 3.6–5.3$. D. Stefanidis and W. P. Jencks, *J. Am. Chem. Soc.*, 1993, **115**, 6045.
37 K. Bowden, *Adv. Phys. Org. Chem.*, 1993, **28**, 171.
38 H. Neuvonen, *J. Chem. Soc.*, *Perkin Trans. 2*, 1990, 669.
39 C. Reichardt, *Solvents and Solvent Effects in Organic Chemistry*, VCH, Weinheim, 2nd edn., 1988, p. 408.
40 L. T. Kanerva, *J. Chem. Soc.*, *Perkin Trans. 2*, 1986, 1433.
41 H. Neuvonen, *J. Chem. Soc.*, *Perkin Trans. 2*, 1986, 1141.
42 P. Greenzaid, Z. Luz and D. Samuel, *J. Am. Chem. Soc.*, 1967, **89**, 749.
43 J. Fastrez, *J. Am. Chem. Soc.*, 1977, **99**, 7004.
44 J. P. Guthrie, *Can. J. Chem.*, 1975, **53**, 898.
45 M. R. Crampton, *J. Chem. Soc.*, *Perkin Trans. 2*, 1975, 185.
46 D. L. Leussing, *J. Org. Chem.*, 1990, **55**, 666.

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