Mechanism of the Reaction of Trialkyl Phosphites with α-Halogenoacetophenones in Alcoholic Solvents

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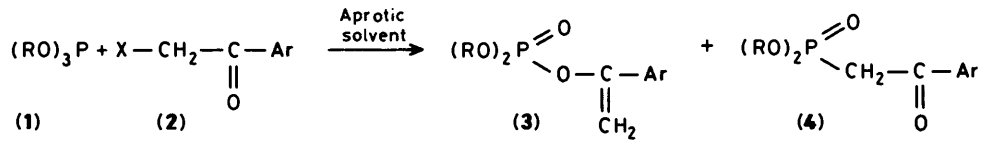
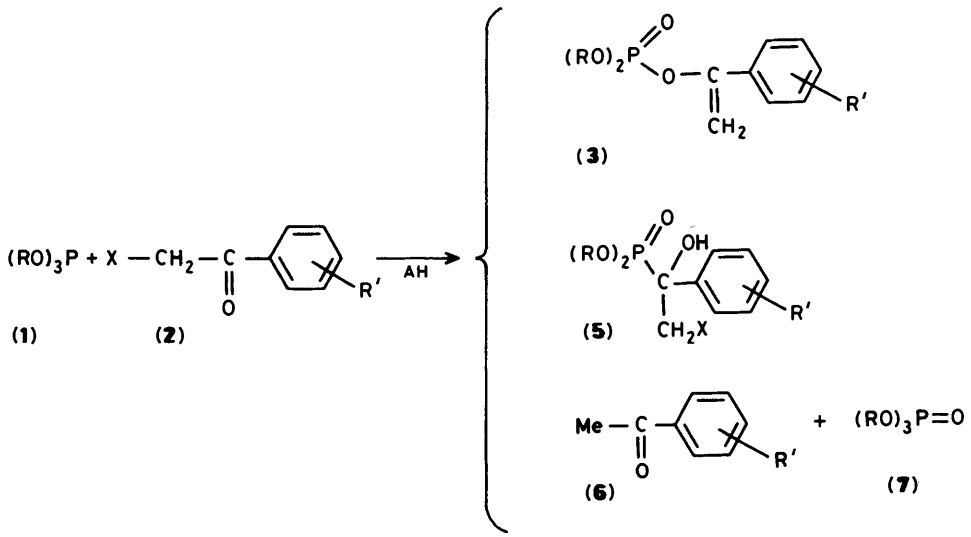
Second-order rate constants and activation parameters have been determined for the reactions of trialkyl phosphites in alcoholic media with α-chloro- or α-bromo-acetophenones having various substituents in the benzene ring (3,4-Me_2, 4-Me, H, 4-Cl, and 4-I). Linear Hammett plots are consistent with the involvement of a common first intermediate in the rate-determining stage, leading to the formation of vinyl phosphate, α-hydroxyphosphonate, and acetophenone. The results provide the first kinetic evidence in support of the initial formation of the previously suggested betaine as a common intermediate in alcoholic solution. Further reaction then involves rearrangement to give the vinyloxyphosphonium species (and hence the Perkow product) or protonation followed by dealkylation to give the α-hydroxyphosphonate. Evidence for the possible formation of dehalogenated ketone *via* solvolysis of the α-hydroxyphosphonium intermediate is also presented.

Reactions of trialkyl phosphites (**1**) with α-halogenoacetophenones (**2**) in aprotic solvents are known to proceed in two possible directions giving varying proportions of the vinyl phosphate (**3**) and β-ketophosphonate (**4**) according to conditions (Scheme 1).[1,2] We have previously investigated the kinetics of these reactions in detail and have postulated a first common intermediate.[3] In reactions with sterically hindered phosphite esters, separate Arbuzov (ketophosphonium) and Perkow (vinyloxyphosphonium) intermediates have been isolated or identified[4] but it is clear that neither is common to both reaction pathways. Any common intermediate must therefore precede the formation of these.

Reactions of the above mentioned components in protic solvents are known to favour vinyl phosphate formation and may also give the α-hydroxyphosphonate (**5**) together with dehalogenated ketone (**6**), trialkyl phosphate (**7**) (Scheme 2),



Scheme 1.



Scheme 2.

Table 1. Product composition and rate constants for the reactions of (1) with (2) in alcohols[a]

Substituents in (1) and (2)			0 °C				26 °C (*15 °C)			
R and X		R′	(6)	(5)	(3) (mol %)	10^4k (dm^3 mol^{-1} s^{-1})	(6)	(5)	(3) (mol %)	10^4k (dm^3 mol^{-1} s^{-1})
Me	Cl	3,4-Me$_2$	7	41	52	0.67	6	27	67	3.03
		4-Me	8	39	53	1.15	7	25	68	4.71
		H	10	35	55	3.26	7	23	70	17.5
		4-Cl	12	30	58	8.51	9	18	73	33.9
		4-I	12	29	59	9.29	8	18	74	40.8
Et	Cl	3,4-Me$_2$	4	13	83	1.11	3*	11	86	3.16
		4-Me	4	13	83	2.05	3	11	86	4.70
		H	4	11	85	6.02	3	10	87	14.5
		4-Cl	4	10	86	15.7	3	9	88	41.0
		4-I	4	9	87	18.1	3	8	89	47.0
Pr^i	Cl	3,4-Me$_2$					0	0	100	5.76
		4-Me					0	0	100	8.15
		H					0	0	100	23.9
		4-Cl					0	0	100	62.7
		4-I					0	0	100	74.7
Me	Br	3,4-Me$_2$	7	10	83	5.12	6	7	87	19.9
		4-Me	7	10	83	6.33	6	7	87	24.3
		H	8	8	84	10.4	7	5	88	44.4
		4-Cl	9	6	85	18.8	7	4	89	76.3
		4-I	9	6	85	23.0	7	4	89	103
Et	Br	3,4-Me$_2$	3	5	92	6.14				
		4-Me	3	4	93	7.36				
		H	3	4	93	15.9				
		4-Cl	3	4	93	30.0				
		4-I	3	3	94	33.0				

[a] The R group of the alcohol (ROH) is in each case the same as in (1).

Table 2. Product compositions and rate constants for the reactions of α-chloro- and α-bromo-acetophenone (2; R = H′) with trimethyl phosphite in protic and aprotic solvents at 26 °C

Solvent	(2; R′ = H)	Products (mol %)	10^4k (dm^3 mol^{-1} s^{-1})	$\frac{k_{Methanol}}{k_{Toluene}}$
Toluene	X = Cl	(3) (100)	0.125	140
Methanol	X = Cl	(3) (70), (5) (23), (6) (7)	17.5	
Toluene	X = Br	(3) (68), (4) (32),	0.218	204
Methanol	X = Br	(3) (88), (5) (5), (6) (7)	44.4	

and other products in certain cases.[2,5–7] β-Ketophosphonates are formed to a lesser extent and were not detected in our investigations.[8] We now report the first kinetic studies to be made for these reactions in alcoholic media and discuss the implications of the results in this field of chemistry.

Results and Discussion

Reactions of trialkyl phosphites with α-halogenoacetophenones were followed in alcoholic solution by the use of gas chromatography (see Experimental section). Before making kinetic measurements, an examination was made of the side reactions which might be expected to occur between the solvent and either of the reactants. Alcohols were thus found to yield hemiacetals and acetals by reaction with the halogeno-acetophenone but the rates were slower on average by two orders of magnitude than for the main reactions studied.[9] Possible complications arising from alcoholysis of the trialkyl phosphite were avoided by the use of alcohol and phosphite in which the alkyl groups were the same. Finally, the trialkyl phosphite undergoes conversion into dialkyl phosphite and into dialkyl alkylphosphonate under reaction conditions (possibly in part because of the dealkylation ability of halide anion[10] formed in the course of reaction) although the error arising from this is negligible if the reaction is run with a high excess of phosphite and can further be diminished by calculating rate constants from the initial points of the rate plot.

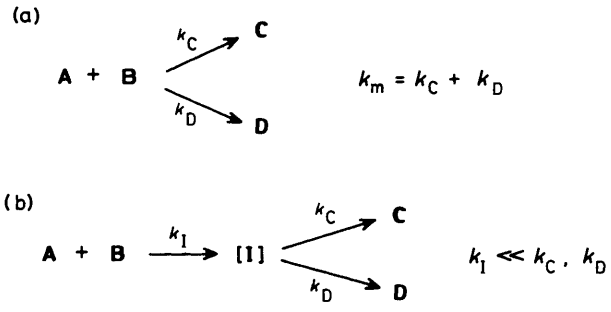
The rate of disappearance of α-halogenoacetophenone in the presence of an excess of phosphite was therefore determined and gave pseudo-first-order rate constants from which overall second-order rate constants were calculated. The kinetic order for trialkyl phosphite was shown to be first in separate experiments. Table 1 shows the calculated k values and the product compositions under various conditions. For comparison purposes we obtained the data for the reactions of α-chloro- and α-bromo-acetophenone with trimethyl phosphite in both aprotic and protic solvents. The reaction rates in protic solvents are higher by about two orders of magnitude than those in aprotic solvents (Table 2).[2] The qualitative effects of structural variation on product composition have been discussed recently.[8] Thus, electron-attracting substituents in the aromatic ring increase both the overall rate and the yield of vinyl phosphate and acetophenone, while the relative amount of α-hydroxyphosphonate decreases. With increasing bulkiness of the alkyl group the relative yield of the vinyl phosphate increases and this is the only product in the case of tri-isopropyl phosphite. Rates are higher with bromoacetophenones than with chloroacetophenones and in the latter case more α-hydroxyphosphonate and acetophenone are formed. At lower temperatures the reaction results in the formation of more α-hydroxyphosphonate and acetophenone (Table 1).

To get a better insight into the nature of the processes involved, Hammett diagrams have been made from the data using the appropriate σ_p values.[11] Good quality straight lines

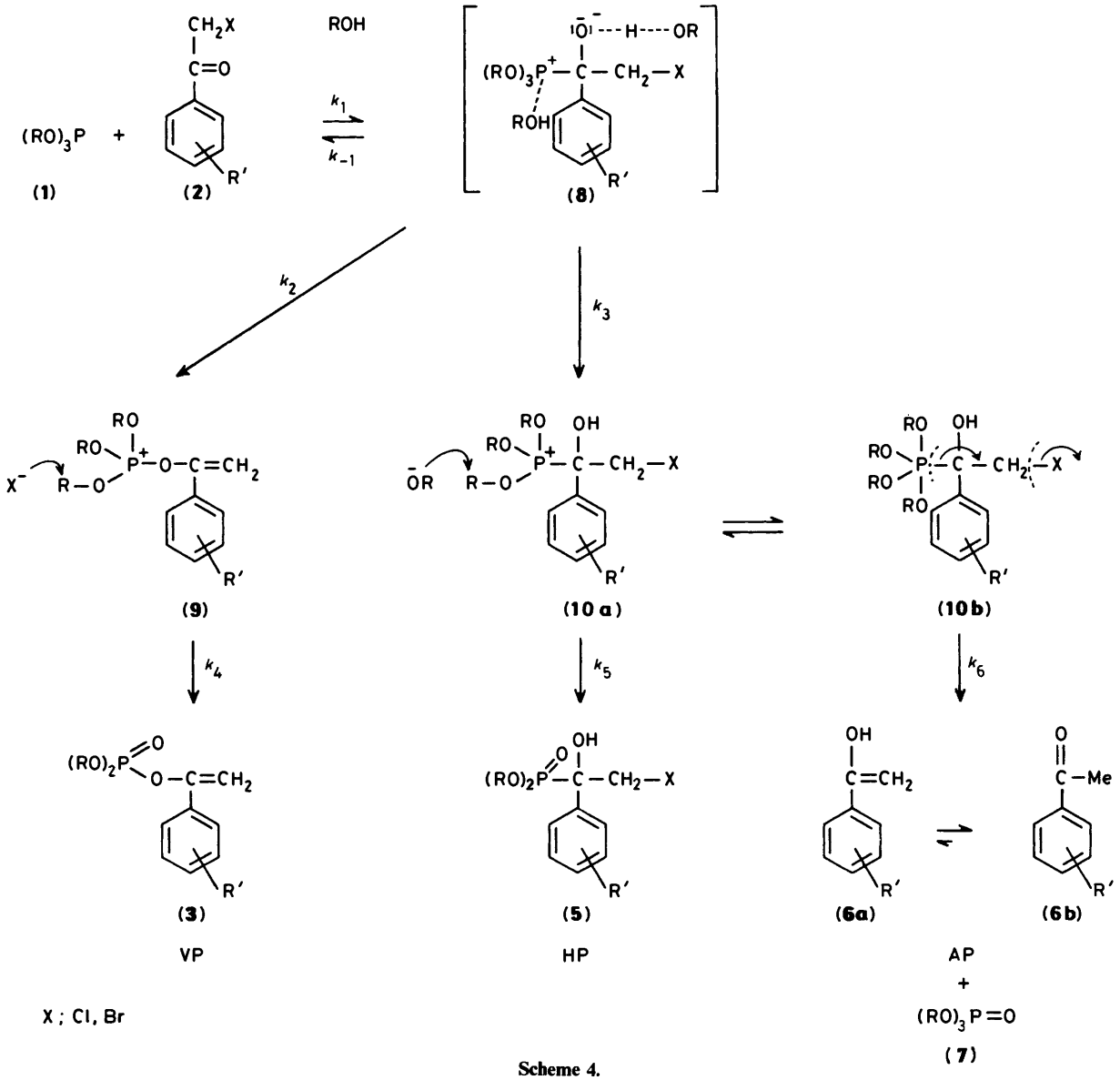
(characterised by r and s) were thus obtained for the reactions of bromoacetophenones with phosphites in alcohols (Figure 1) and from this fact we conclude that a common intermediate is involved in the rate-determining step for the formation of all three products: vinyl phosphate, α-hydroxyphosphonate, and acetophenone, and that the further reactions leading to products are faster.

Parallel reactions, as illustrated in Scheme 3, will only be expected to give straight line plots if pathway (b) is followed. For pathway (a), plots of log k_C and of log k_D *versus* σ should separately be linear and it follows in this case that some deviation from linearity must occur if log $(k_C + k_D)$ is plotted. As the hydroxyphosphonate can only be formed by attack of the phosphite on the carbonyl carbon of the halogenoacetophenone, the common intermediate is assumed to have the betaine structure, probably stabilised through hydrogen bonding to the solvent (**8**) (Scheme 4). Whereas the formation of hydroxyphosphonate in protic media has previously been taken to indicate the formation of a betaine precursor, the result did not provide compelling evidence that the betaine must also be an intermediate on the pathway to vinyl phosphate formation.[2] Our results provide the first kinetic evidence that this is so.

The magnitude and positive sign of the ρ-values for these reactions (ρ = 1.23—1.44, Table 3) are in agreement with nucleophilic attack of the phosphite on the carbonyl carbon atom in the rate-determining step (*cf.* ref. 12 for analogous reactions), and the large negative values of the activation entropies (Table 4) are also in accord with the formation of a betaine intermediate. This intermediate may then be expected to rearrange to the vinyloxyphosphonium intermediate (**9**) and



Scheme 3.

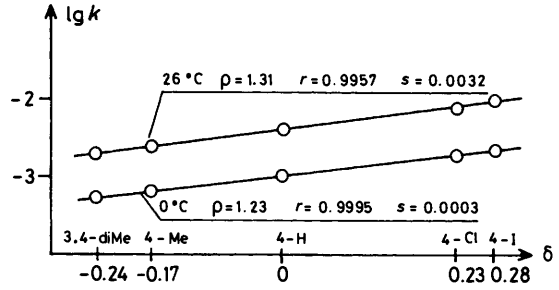


Scheme 4.

Table 3. Hammett ρ-values for the reactions of α-halogenoacetophenones (2; R′ = H) with trialkyl phosphites (1)

Substituents in (1) and (2) (R′ = H)		Solvent	T (°C)	ρ
R = Me	X = Cl	MeOH	0	2.84*
		MeOH	26	3.20*
R = Et	X = Cl	EtOH	0	2.76*
		EtOH	15	2.77*
R = Me_2CH	X = Cl	PriOH	26	2.62*
R = Me	X = Br	MeOH	0	1.23
		MeOH	26	1.31
R = Et	X = Br	EtOH	0	1.44

* These values were calculated from three points.



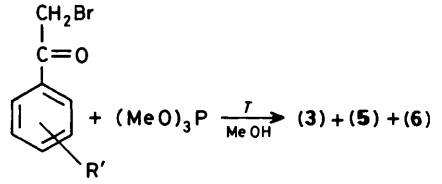


Figure 1.

thence to give the vinyl phosphate (**3**), as proposed,[2] or it may become protonated by the solvent to give (**10**) leading to the hydroxyphosphonate (**5**).

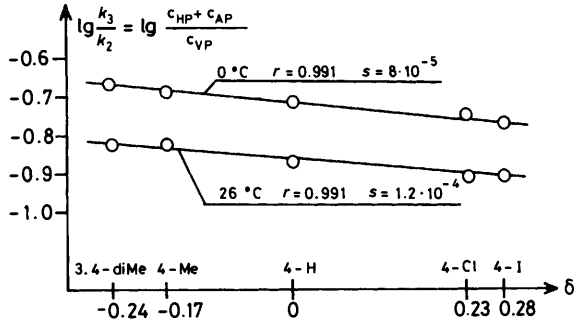
Our results also suggest that the dehalogenated ketone (**6**) and trialkyl phosphate (**7**) may be formed by solvolysis of the α-hydroxyphosphonium intermediate (**10**) as shown (Scheme 4). This is a novel proposal, supported by a consideration of the effect of the leaving ability of the halogen. An increase in leaving ability (Cl < Br) thus leads to an increase in the proportion of (**3**) formed at the expense of both (**5**) and (**6**) (Table 5) and a similar trend is followed on increasing the temperature. Within a decreased sum of (**5**) and (**6**), however, the proportion of dehalogenated ketone increases. Linear Hammett plots of log $(C_5 + C_6)/C_3$ and of log C_5/C_6 *versus* σ (Figures 2—5) are also consistent with the parallel formation of (**5**) and (**6**) by one route and of (**3**) by a separate route (*cf.* ref. 13) and are characterised by better correlation coefficients than are obtained for other possible combinations of routes from the intermediate (**8**). On this basis, the formation of dehalogenated ketone by solvolysis of the vinyloxyphosphonium species (**9**) is excluded. Another potential route for the formation of dehalogenated ketone involves solvolysis of the halogenophosphonium enolate ion-pair, formed by attack of trialkyl phosphite on the halogen of the α-halogenoacetophenone.[5c] This route is particularly significant in the reactions of trialkyl phosphites with α,α-dibromo- or α-bromo-α-phenyl-acetophenones in acetic acid,[6] and in the reactions of sterically hindered α-bromo- and α,α-dihalogenoacetophenones in methanol.[7] Such a route is not necessarily involved, however, in the systems reported here. It is not consistent with the kinetic evidence for a common first intermediate and is particularly unlikely in the reactions of the α-chloroacetophenones. We have furthermore shown that the unsubstituted acetophenone is formed as a product in the reaction of trimethyl phosphite with

Table 4. Activation parameters for the reactions of α-halogenoacetophenones (2) with trialkyl phosphites (1) in alcoholic media (and in toluene*[2a])

Substituents in (1) and (2)		$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J mol^{-1} K^{-1})
R = Me	X = Cl, R′ = 3,4-Me_2	36.9	−188.5 (−169.7*)
	R′ = 4-Me	34.4	−193.1 (−164.7*)
	R′ = H	41.2	−159.7 (−165.1*)
R = Et	X = Cl, R′ = 3,4-Me_2	43.2	−161.3
	R′ = 4-Me	33.8	−190.6
	R′ = H	35.9	−173.9
R = Me	X = Br, R′ = 3,4-Me_2	33.0	−186.0
	R′ = 4-Me	32.7	−185.2 (−176.8*)
	R′ = H	35.4	−171.0 (−209.8*)
	R′ = 4-Cl	34.2	−171.0 (−149.6*)
	R′ = 4-I	36.7	−159.7

Table 5. Dependence of rates of product formation on the leaving ability of halogen in the reactions of α-chloro- and α-bromo-acetophenone (2; X = Cl or Br, R′ = H) with trialkyl phosphites (1) in alcohol

Substituents in (1) and (2)				
R	X	T (°C)	(3)/[(5) + (6)]	(6)/(5)
Me	Cl	0	1.2	0.28
	Br		5.3	1.0
	Cl	26	2.3	0.3
	Br		7.3	1.4
Et	Cl	0	5.7	0.36
	Br		13.3	0.75



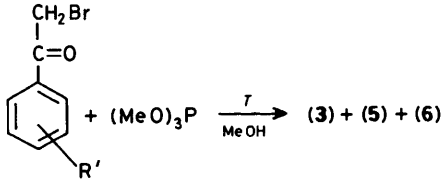


Figure 2.

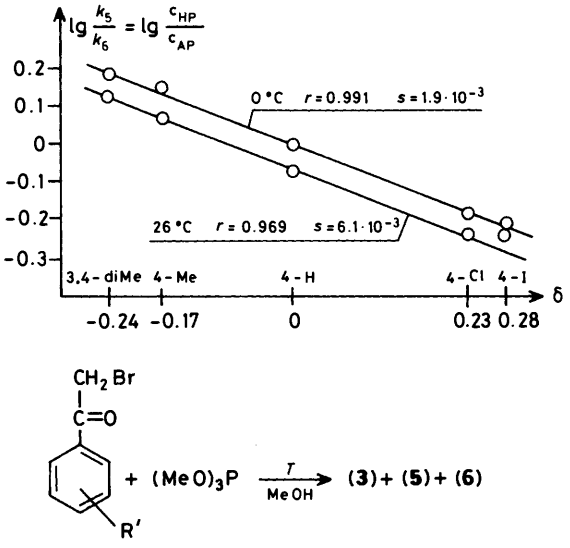


Figure 3.

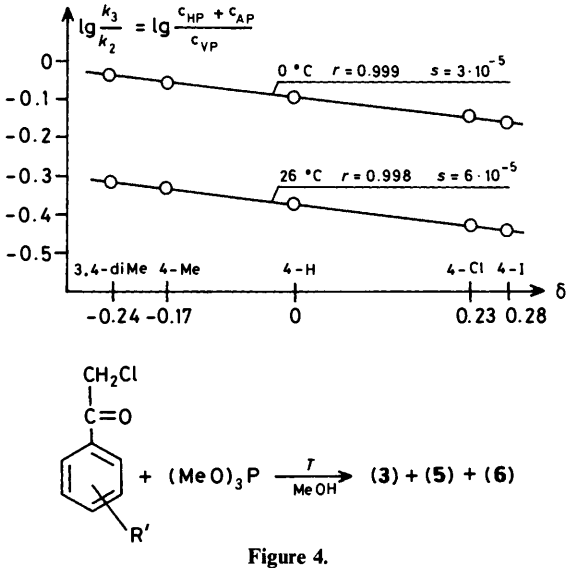


Figure 4.

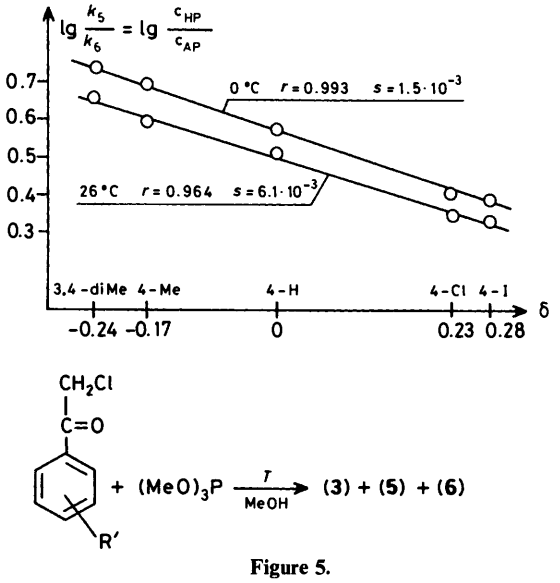


Figure 5.

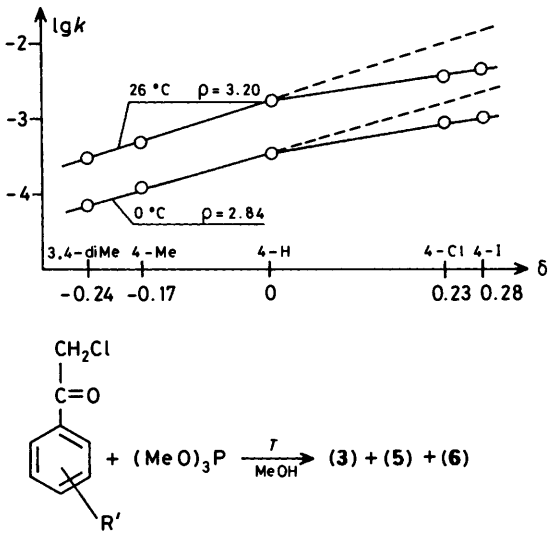


Figure 6.

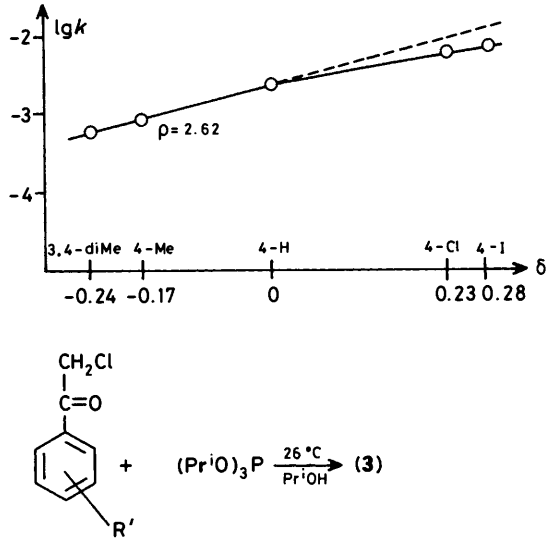


Figure 7.

α-tosyloxy-4′-methylacetophenone in methanol, a reaction system in which a halogenophosphonium enolate (or analogous intermediate) cannot be involved.[14]

As can be seen from Figures 6 and 7 the Hammett plots for the reactions of the chloroacetophenones (**2**; X = Cl) with trialkyl phosphites become curved in the region of compounds having electron-attracting substituents ($\sigma_p > 0$) in the aromatic ring. It may also be noted that a curved plot is obtained for the reaction of α-chloroacetophenone with tri-isopropyl phosphite in isopropyl alcohol although vinyl phosphate is the only product in this case. These observations are consistent with reversibility of the first rate-determining step of the reaction. Otherwise, the same overall mechanism is assumed to apply for the reactions of both α-chloro- and α-bromo-acetophenones.

Experimental

Starting materials, the preparations of α-halogenoacetophenones, vinyl phosphates, and α-hydroxyphosphonates, and gas chromatographic procedures, were as previously described.[3,8,12c] Kinetic measurements were carried out in a thermostatted bath (±0.1 °C). Trialkyl phosphite was added

Table 6. Conditions for pseudo-first-order kinetics

Substituents in (1) and (2) (R′ = H)		Solvent	[(1)]/[(2)]	[(1)] (mol dm^{-3})
X = Cl	R = Me	MeOH	20	1.06
	R = Et	EtOH	20	0.70
	R = Me_2CH	Pr^iOH	15	0.48
X = Br	R = Me	MeOH	15	0.55
	R = Et	EtOH	15	0.55
X = OTs	R = Me	MeOH	20	0.76

to the mixture of α-halogenoacetophenone (2.5 mmol) and alcohol with vigorous stirring. Experiments were carried out under pseudo-first-order conditions by keeping the trialkyl phosphite in a large excess as summarised in Table 6. First-order rate constants were obtained for the disappearance of α-halogenoacetophenone (corrected for that produced under g.l.c. conditions by decomposition of the α-hydroxyphosphonate)[8] and were used to calculate overall second-order rate constants, k. Rate ratios for individual reactions within Scheme 4 were calculated from product composition ratios which did not vary throughout the course of reaction. Thus $k_3/k_2 = (C_{HP} + C_{AP})/C_{VP}$ and $k_5/k_6 = C_{HP}/C_{AP}$. Values for r and s were calculated using the least-squares treatment. Activation parameters were calculated from the Arrhenius equation.

Preparation and Reaction of α-Tosyloxy-4′-methylacetophenone.—By a similar procedure to that described for the preparation of other α-keto toluene-*p*-sulphonates,[14] α-tosyloxy-4′-methylacetophenone was obtained in 61% yield, m.p. 90—91 °C; $\delta_H(CDCl_3)$ 2.39 (s, Me), 2.41 (s, Me) (partially overlapping, 6 H), 5.19 (s, 2 H, CH_2), 7.10—7.95 (m, 8 H, Ar); $\nu_{max.}$ (KBr) 800 (C–HAr), 1 340 (S=O), 1 595 (C=C), 1 695 cm^{-1} (C=O). Reaction with trimethyl phosphite in methanol was carried out under the conditions shown (Table 6). After 3 h at room temperature g.l.c. analysis showed the formation of 4-methylacetophenone (**6**; R′ = 4-Me) (45%) and dimethyl 1-(*p*-tolyl)vinyl phosphate (**3**; R = Me) (20%).

Acknowledgements

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