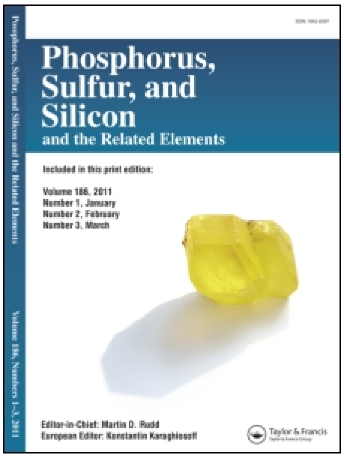

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KINETIC STUDY OF THE HORNER-REACTION. II

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KINETIC STUDY OF THE HORNER-REACTION. II

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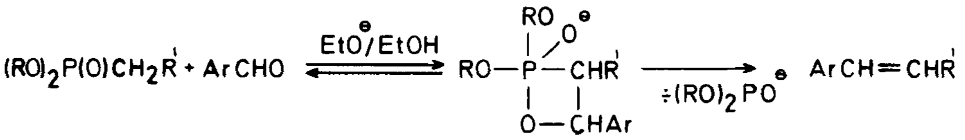
The results of the kinetic study of the Horner-reaction between *m*- and *p*-substituted benzaldehydes and two 2-carbethoxymethyl-substituted phosphinates (III and IV), and corresponding phosphine oxides (V and VI) in ethanolic sodium ethoxide are reported. The kinetics of the reactions are overall third order, first order in aldehyde, ethoxide and phosphinate, or phosphine oxide.

The rates of the reaction are found to be increased by electron-withdrawing substituents in the benzaldehydes, in accordance with a rate-determining addition of the phosphoryl stabilized carbanion to the carbonyl group in the aldehydes. Phosphinate (III) are found to react about 35 times faster than the analogous phosphine oxide (V), in spite of the nearly equal *pK*-values of the two compounds. This rate effect is discussed in terms of their ability, in the reactions with aldehydes, to form a pentacoordinated intermediate. Within each group of compounds, the rate of the reaction is found to increase with increasing basicity of the phosphoryl stabilized carbanion.

INTRODUCTION

In a previous paper we reported a kinetic study of the Horner-reaction between *m*- and *p*-substituted benzaldehydes and five phosphonates in ethanolic sodium ethoxide[1]:



The kinetics of the reactions were overall third order, first order in each of phosphonate, aldehyde and ethoxide. The rate of the reactions were found to be increased by electron-withdrawing *m*- and *p*-substituents attached to the aromatic ring in the aldehyde. This was reflected in a reaction constant, ρ, of $+1.95$ when $\log(k/k_0)$ values were plotted against the appropriate Hammet σ-constants for the reaction between 2-carbethoxymethyldiethylphosphonate (I) and various *m*- and *p*-substituted benzaldehydes.

A large rate increase was observed in the reactions between substituted benzaldehydes and the five-membered cyclic analogue of (I), the 2-carbethoxymethyl-4,5-dimethyl-2-oxo-1,3,2-dioxaphospholane (II).

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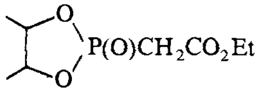
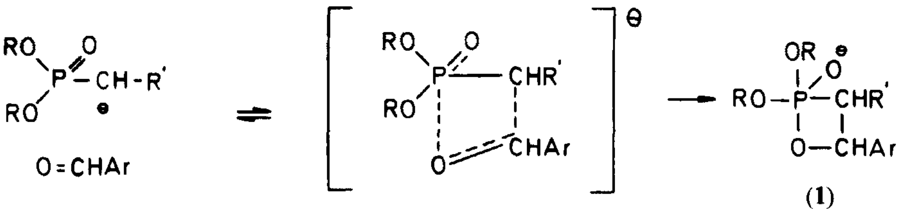
(EtO)$_2$P(O)CH$_2$CO$_2$Et

(I)



(II)

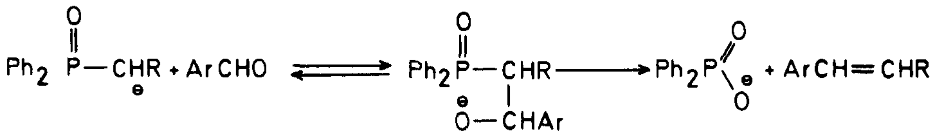
It was concluded that the results obtained could best be explained in terms of a rate-determining nucleophilic attack of the phosphoryl-stabilized carbanion on the carbonyl carbon in the aldehyde, with a nearly simultaneous P—O bond formation, which leads directly to the pentacovalent intermediate (**1**):



(**1**)

In a further study we were interested to evaluate the rate effects in the same type of reaction of phosphinates and phosphine oxides.

Horner *et al.*[3] were the first to explore the generation of a carbanion from a phosphine oxide and its subsequent reaction with carbonyl compounds to olefins. They also proposed a mechanism similar to the Wittig-reaction. The carbanion of phosphine oxide (**2**) attacks the carbonyl carbon in a reversible step to afford a "betaine" (β-oxy-phosphine-oxide-intermediate) (**3**):

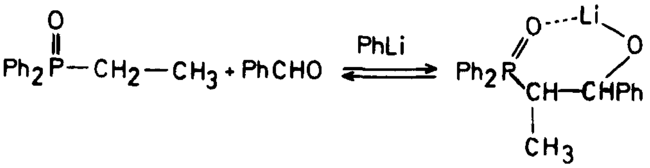


(**2**) (**3**) (**4**)

An intramolecular rearrangement of (**3**) gives rise to olefin and phosphinate anion. The driving force in the reaction is assumed to be the formation of the new phosphorus–oxygen bond in the phosphinate-anion (**4**).

Some β-hydroxy-phosphine oxides have been isolated after reacting carbanions of phosphine oxides with carbonyl compounds in presence of strong complexing agents, e.g. lithium-ions, and this has been taken as evidence that the reaction is proceeding via "betaines" (**3**) to olefins.[4, 5]

Schlosser *et al.*[6] have also, by ^{31}P-NMR, demonstrated the intermediacy of a "betaine" (**5**) in the reaction of diphenyl ethyl phosphine oxide and benzaldehyde in presence of phenyl lithium:



(5)

$\delta_{^{31}P}$ = 36 ppm (downfield from 65% H_3PO_4)

However, to our knowledge, no intermediates have been detected or isolated in the Horner reaction in the absence of complexing agents or when there is a strong electron-withdrawing group (e.g. —C≡N, —CO_2R, —COR) linked to the α-carbon in the phosphine oxides.

In the following we report the results of a kinetic investigation of the reaction between various *m*- and *p*-substituted benzaldehydes and two phosphinates and phosphine oxides in ethanolic sodium ethoxide.

(III) $Ph(EtO)P(O)CH_2CO_2Et$,
(IV) $n\text{-}Bu(EtO)P(O)CH_2CO_2Et$
(V) $Ph_2P(O)CH_2CO_2Et$,
(VI) $n\text{-}Bu_2P(O)CH_2CO_2Et$

RESULTS AND DISCUSSION

The reactions of (III–VI) with substituted benzaldehydes in ethanolic sodium ethoxide gave the corresponding ethyl cinnamates in good yield (80–100%). By varying the concentrations of each of the reactants it was found that the reactions were overall third order, first order in phosphinate resp. phosphine oxide, aldehyde and ethoxide.

The reactions of phosphinate (IV) and phosphine oxide (VI) were also followed by monitoring the decrease in aldehyde concentration and the increase in olefin concentration simultaneously during the reactions. This procedure was not practicable with phosphinate (III) and phosphine oxide (V) owing to the very strong UV-absorption of (III) and (V) in the region of the aldehyde absorption (230–260 nm). Figure 1 shows the UV-spectra of the reaction solution recorded periodically in the reaction between benzaldehyde and phosphinate (IV), and in Fig. 2 are the resulting first order rate plots for consumption of aldehyde and production of olefin. Similar results were obtained in the reaction between phosphine oxide (VI) and *p*-chloro-benzaldehyde.

The similar rates and the well-defined isobestic point in Fig. 1 strongly indicates that there are no detectable accumulation of intermediates in the reaction under the present reaction conditions.

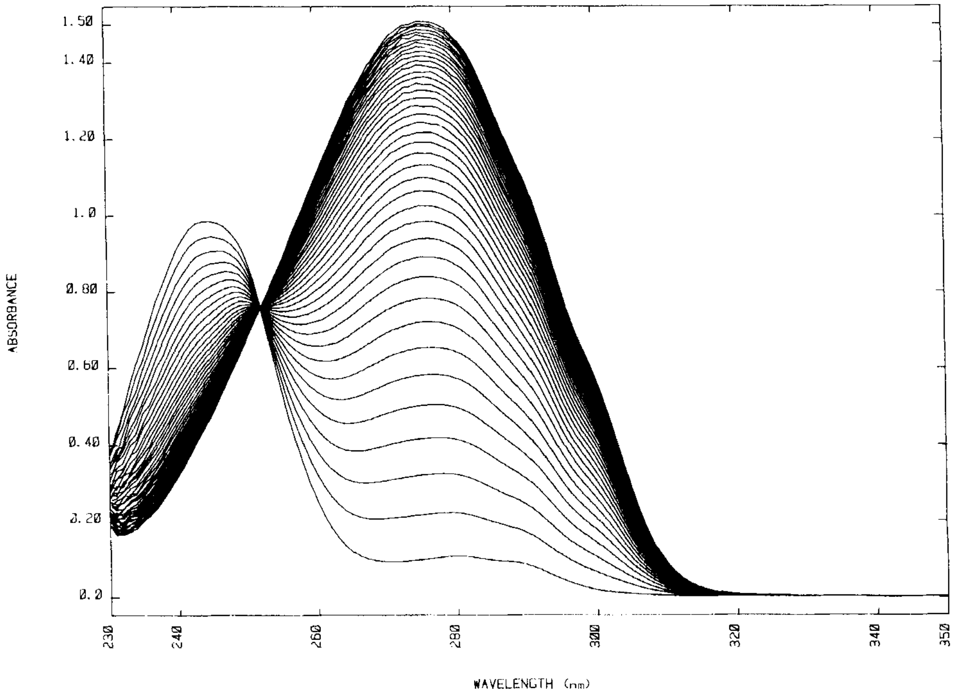


FIGURE 1 UV-spectra of the reaction between (IV) and benzaldehyde at 30.0°C, scanned every 150 sec.

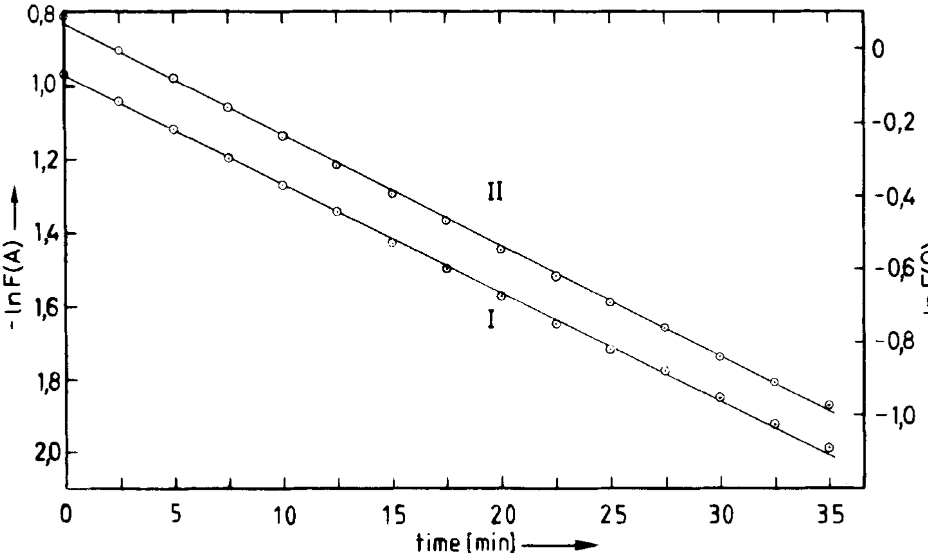
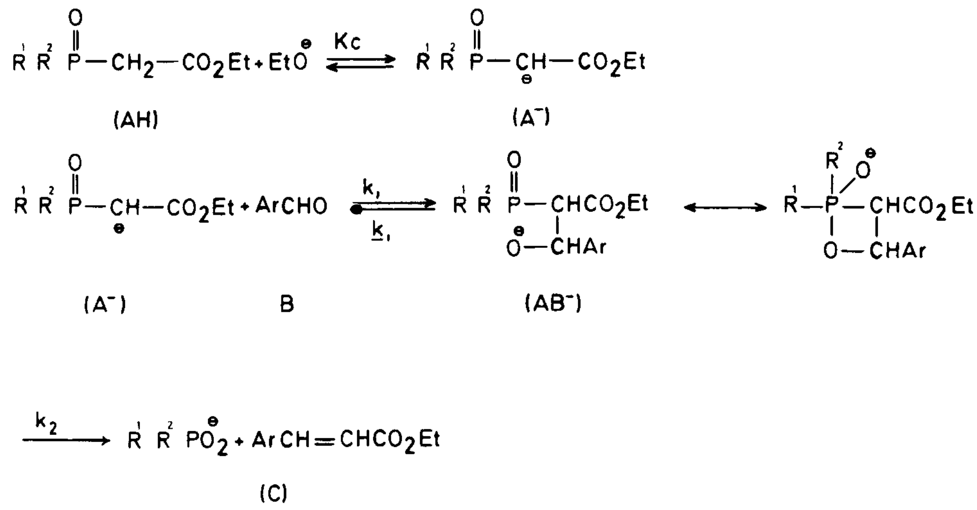


FIGURE 2 Pseudo 1. order rate plots of the reaction between (IV) and benzaldehyde at 30.0°C (See Fig. 1). Curve (I) is the rate plot of ln F(A) = $\ln(A_{t+\Delta} - A_t)$ vs. time based on the absorbance data of benzaldehyde (λ = 245 nm), k_{obs} = 4.89 ($\pm$0.09) $\times 10^{-4}$ s^{-1}. Curve (II) is the plot of ln F(0) = $\ln(A_{t+D} - A_t)$ vs. time based on the absorbance data of ethyl cinnamate (λ = 275 nm), k_{obs} = 5.05 ($\pm$0.06) $\times 10^{-4}$ s^{-1}.

The data thus confirm that the phosphinates as well as phosphine oxides react with benzaldehydes according to the same kinetic scheme previously proved for phosphonates:



SCHEME 1

From Scheme 1, the following rate expression results[14]:

$$\text{Rate} = \frac{k_1 k_2}{k_{-1} + k_2} K_c [\text{AH}][\text{B}][\text{EtO}] = k' K_c [\text{AH}][\text{B}][\text{EtO}] \qquad \text{(a)}$$

K_c is the equilibrium constant for the first acid-base equilibrium and is given by the ratio K_a/K_{EtOH} where K_a is the acid dissociation constant of AH in ethanol and $K_{\text{EtOH}} = 10^{-18.9}$ the autoprotolysis constant of ethanol.[15]

In Table I are recorded the rate data for the reactions of phosphinate (III) and phosphine-oxide (V) with various substituted benzaldehydes. Hammet plots of the rate data reveals that the rate of reaction is increased by electron-withdrawing *m*- and *p*-substitutents attached to the aromatic ring in the aldehydes. This is reflected in the positive reaction constants when $\log(k/k_0)$ values are plotted against the appropriate σ-constants.

By comparing the results of such plots for (III) and (V) with the previously studied phosphonate, (I), ($\rho = 1.95$), it is seen that there is an increase in the reaction constant, ρ, when an alkoxy group is successively substituted by a phenyl group. When the oxygen atom in phosphine oxide (V) is replaced by a phenyl group, the reaction constant is further increased. The reaction constant for the reaction of 2-carbethoxymethyl triphenylphosphorane with various *m*- and *p*-substituted benzaldehydes is +2.9 in acetonitril at 20.0°C.[16]

The successively higher ρ-values in the series from phosphonates to phosphonium salts may reflect less nucleophilicity of the corresponding carbanions or greater steric hindrance in the rate-determining step. The higher reactivity of carbanions of phosphonate and phosphine oxide towards electrophilic centra, as compared to the

TABLE I

Rate constants for the reaction (at 20.0°C).

$$\underset{\text{III and V}}{R^1R^2P(O)CH_2CO_2Et} + x\text{-}C_6H_4CHO \xrightarrow{1B} R^1R^2PO_2^- + x\text{-}C_6H_4CH = CHCO_2Et$$

		k' [l M^{-1} s^{-1}]		$\log(k'_x/k'_0)$	
x	σ_x	III	V	III	V
p-NO_2	0.78	449.9	12.59	1.55	1.70
m-Cl	0.40	89.18	2.24	0.85	0.95
p-Cl	0.23	111.8	0.93	0.52	0.57
m-MeO	0.10	13.90	0.383	0.05	0.18
H	0	12.54	0.251	0	0
m-Me	−0.07	8.16	0.159	−0.19	−0.20
p-Me	−0.17	3.66	0.0718	−0.53	−0.54

Reaction constant, ρ: 2.16 2.33
Correlation coefficient, r: 0.993 0.996

analogous triphenyl phosphoranes, are well known,[2] and has also been demonstrated by Horner *et al.*[17] in direct competition experiments.

In Table II are recorded the rate constants for the reactions of (III–VI) with p-nitrobenzaldehyde. The rate data for the diethylphosphonate analogue are also included. As the results show, there is a relatively small rate decrease from phosphonate (I) to phosphinate (III), and a very large drop in rate from the phosphinate to the corresponding diphenylphosphine oxide (V) in their reactions with p-nitro benzaldehyde.

The nearly identical pK_a-values of (III) and (V), both in ethanol[13] and in other media,[10] point to similar electronic effects in the carbanions derived from (III) and (V). The steric requirements for a rate-determining attack of these carbanions on the

TABLE II

Rate constants for the reaction (at 20.0°C).

$$\underset{\text{III and VI}}{R^1R^2P(O)CH_2CO_2Et} + p\text{-}NO_2\text{—}C_6H_4CHO \xrightarrow{1B} p\text{-}NO_2\text{—}C_6H_4CH = CHCO_2Et + R^1R^2PO_2$$

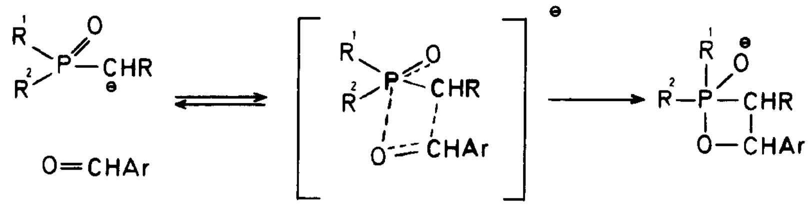
	R^1	R^2	$k^1 \times 10^{-1}$ [l M^{-1} s^{-1}][a]	pK_a
I	EtO	EtO	386[b]	19.75
III	Ph	EtO	45.0	19.50
IV	n-Bu	EtO	56.5	20.30
V	Ph	Ph	1.26	19.40
VI	n-Bu	n-Bu	17.5	21.20

[a] Calculated from Eq. 1 with $K_c = K_a/K_{EtOH}$.
[b] Taken from ref. 1.

carbonyl carbon is not expected to be very different since the substitution is relatively far removed from the reaction centre, and therefore the rate ought to be relatively unaffected by the substitution. A rate-controlling "betaine" decomposition (k_2 in Scheme 1) is not consistent with the observed positive values for ρ in the reactions. A negative ρ-value would be predicted for "betaine" decomposition and the net effect of substitution on the aromatic ring would be small and of unpredictable sign.[18]

Substitution of *n*-butyl for phenyl in the carbanions of phosphine oxide will enhance the reactivity of the carbanions derived from (VI) due to the greater basicity of the carbanions of dibutyl phosphine oxide (VI), and increase k_1 in the reaction (Scheme 1). The same substitution, however, would diminish k_2 since the greater electron-donating capacity of butyl would retard the attack of the "betaine" oxy-anion on the phosphorus atom.[18] As Table II shows, the dibutyl phosphine oxide (VI) reacts about 14 times faster than the diphenyl analogue (V). The large drop in rate on passing from phosphinate (III) to phosphine oxide (V) is therefore not consistent with a change in rate-determining step from a rate-determining k_1 to a rate-controlling "betaine" decomposition.

However, if we assume that the rate-determining step in the reaction consists of direct formation of a pentacoordinated intermediate, the influence of the substituents on the phosphorus atom becomes more noticeable. The steric- and electronic effects of the substituents on the phosphorus atom are increasing upon passing to the pentacoordinated intermediates.[19]



As the stability of the proposed pentacoordinated intermediate will be decreased when alkoxy groups are successively replaced by alkyl or phenyl groups,[19] this destabilizing effect ought to be reflected in the reaction rates. When the last alkoxy group in the phosphinates are substituted by an alkyl- or phenyl group, as in the phosphine oxides (V and VI), their reactions with aldehydes will be relatively unfavourable since C-atoms of low electrophilicity are forced into an apical position of the pentacoordinated intermediate.[20] The four-membered ring highly prefers the apical-equatorial position, and the negatively charged oxygen the equatorial one.[19]

The large drop in reaction rate from phosphinate (III) to phosphine oxide (V) is consistent with this view. The rate effect of passing from phosphonates to phosphinates is smaller, since the phosphinates still contain an alkoxy group which prefers the apical position. The alkyl or phenyl groups occupy the equatorial position where the relative preference between alkyl, phenyl and alkoxy groups are smaller than the relative preference for an apical position.[19-21]

EXPERIMENTAL

Materials. The phosphinates and phosphine oxides were prepared by the Arbuzov-reaction between ethyl-bromoacetate (VII), and the appropriate phosphonites and phosphinites.[7]

Ethyl-phenyl-2-carbethoxymethyl phosphinate, (III). Diethyl-phenyl phosphinate was added to VII at 120°C, and heated at 140°C for 1 hour. Bp. 122–23°C (0.05 mm), n_D^{22} = 1.5080, Reported[8] Bp. 142–48°C (0.9 mm), n_D^{20} = 1.5078.

Ethyl-butyl-2-carbethoxymethyl-phosphinate (IV). Diethyl-butyl-phosphonite[9] and (VII) at 150°C gave (IV) in 60% yield. Bp. 78°C (0.04 mm), n_D^{22} = 1.4465. The compound was found pure on GLC ($>$ 99.5%) and NMR.

Diphenyl-2-carbethoxymethyl-phosphine oxide (V). Ethyl-diphenyl-phosphinite was slowly added to (VII) at 80°C. Keeping the reaction mixture at 120°C for 1 hour, gave (V). After three recrystallizations from hexane the compound melted at 76–77°C. Reported[10] 75.5–76.5°C.

Di-n-butyl-2-carbethoxymethyl-phosphine oxide (VI). Butyl-dibutyl-phosphinite (prepared from *n*-Butyl-dichlorophosphite and 2 eq. *n*-Butylmagnesium chloride, according to the method of Sander[9]) and (VII) gave after 1 hour at 120°C, (VI): Bp. 109°C (0.05 mm), n_D^{22} = 1.4619, Reported[11] Bp. 145–46°C (2 mm), n_D^{22} = 1.4625.

Kinetic measurements. The rate of the reaction of (III–VI) with substituted benzaldehydes in ethanolic sodium ethoxide was determined by following the ultraviolet absorption of the substituted ethyl cinnamates or the reacting aldehydes. The reactions were performed under pseudo 1. order reaction conditions using a spectrophotometric method as previously described,[1] with large excess of phosphoryl compound (III–VI) and ethoxide over aldehyde. A Hewlett Packard HP 8450A UV/VIS Spectrophotometer was used.

Measurements of pK-values. The acidity constants (pK_a) of the phosphinates and phosphine oxides were determined with the same method as used previously for phosphonates.[1] The measurements were performed in mixtures of dimethyl sulphoxide and ethanol according to the stepwise technique described by Dolman and Stewart.[12]

The reported pK_a-values (Table II) are relative to that of diethyl malonate (pK_a = 17.60) determined in ethanol, and are thus referred to ethanol as standard state. Further experimental details may be found elsewhere.[1,13]

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