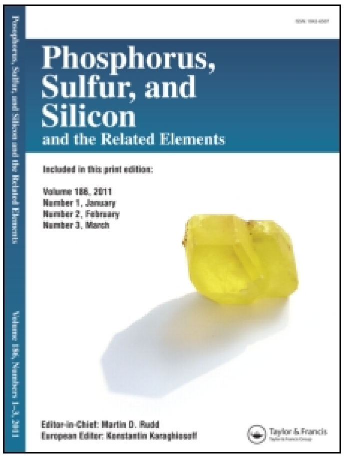


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

KINETIC STUDY OF THE HORNER-REACTION. I

Rolf Olaf Larsen[a][b]; Gunnar Aksnes[a]
[a] Department of Chemistry, University of Bergen, Bergen [b] Norsk Hydro, Research Center, Porsgrunn, Norway

To cite this Article Larsen, Rolf Olaf and Aksnes, Gunnar(1983) 'KINETIC STUDY OF THE HORNER-REACTION. I', Phosphorus, Sulfur, and Silicon and the Related Elements, 15: 2, 219 — 228
To link to this Article: DOI: 10.1080/03086648308073297
URL: http://dx.doi.org/10.1080/03086648308073297

Phosphorus and Sulfur, 1983, Vol. 15, pp. 219–228
0308-664X/83/1502-0219/$18.50/0

KINETIC STUDY OF THE HORNER-REACTION. I

ROLF OLAF LARSEN* and GUNNAR AKSNES

Department of Chemistry, University of Bergen,
Realfagbygget, Allegt. 41, N-5000 Bergen

(Received December 27, 1982)

The rates of the Horner-reaction of five phosphonates (I–V) with sodium ethoxide and various *p*- and *m*-substituted benzaldehydes, and ethanol as solvent, are reported. The kinetics of the reactions are overall third order, first order in phosphonate, ethoxide, and aldehyde, respectively. The reaction is accelerated by electron-withdrawing substituents in the benzaldehyde, giving a reaction constant, ρ, of approximately +2.0. The five-membered cyclic phosphonate (IV) is found to react about 20 times faster than its acyclic analogue (I). The rate difference is attributed to a considerable release in ring strain upon passing from the tetrahedral to the pentacoordinate state in the intermediate of the cyclic phosphonate.

INTRODUCTION

Phosphonate-stabilized carbanions react with aldehydes and ketones giving olefins and dialkylphosphates.[1] The reaction occurs under milder conditions and with a greater variety of carbonyl compounds than the conventional Wittig-reaction due to higher nucleophilicity of phosphoryl-stabilized carbanions.[2] The water-soluble dialkylphosphates formed in the reaction are easily separated from the olefinic products. These advantages over the Wittig-reaction have made the reaction especially attractive, and in the latter years it has come to challenge the Wittig-reaction as the synthetic method of choice when a specific alkene is required.

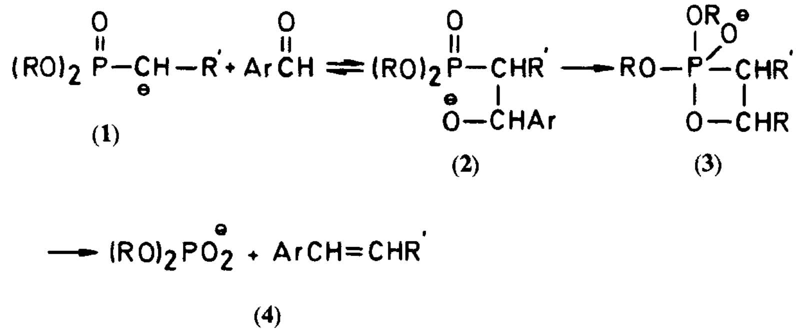
Since 1958, when Horner, Hoffmann and Wippel first described the reaction,[1] several excellent reviews have appeared in the literature,[3–7] dealing with synthetic application as well as mechanism of the reaction. Interest in the mechanism has been focused, especially on factors controlling the stereochemistry of the olefin formed.

Usually the mechanism of the Horner-reaction is discussed in terms of initial and reversible formation of an oxy-anion intermediate (**2**), which collapses to dialkylphosphate and alkene *via* a pentacovalent oxaphosphetane intermediate (**3**)[6] (Scheme 1). The reversible character of the first step has been demonstrated in a number of reactions.[8–11]

In view of the increasing importance of the Horner-reaction in preparative organic chemistry, a kinetic study of the reaction seemed to be of interest. Whereas the kinetics of the Wittig-reaction of phosphonium ylids have been extensively investigated,[12–17] no rate data of the corresponding reaction between phosphoryl-stabilized carbanions and carbonyl compounds are reported. A point of special interest is the postulated intermediate (**2**) in the latter reaction. When strong complexing agents are

---

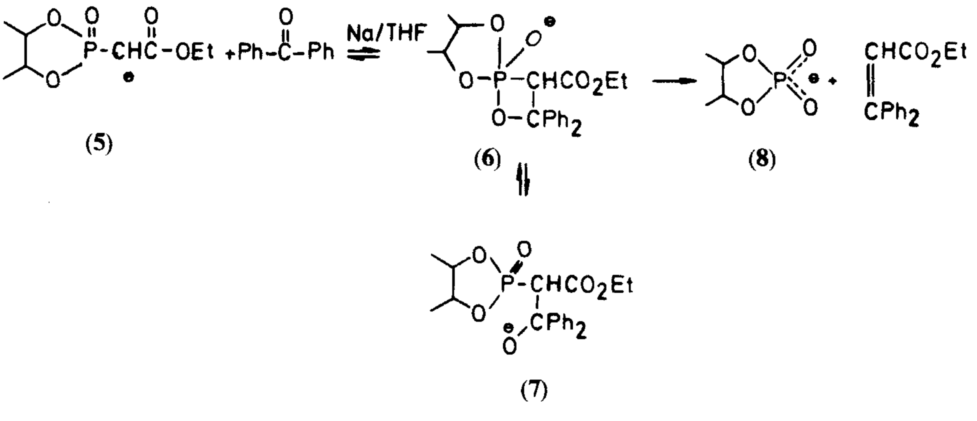
*Address after January 3, 1983: Norsk Hydro, Research Center, N-3900 Porsgrunn, Norway.



SCHEME 1

present in the reaction medium, the reaction can be stopped at stage (**2**), thus allowing the isolation of the β-hydroxyphosphonate.[6,7] However, no sodium or lithium salt of an oxyanion intermediate (**2**) has been isolated when the α-carbon in the alkyl-portion of the phosphonate carries an electron-withdrawing group (e.g. R = $-C{\equiv}N$, CO_2Et).[6,7]

Recently,[18] evidence has been presented that a pentacovalent oxaphosphetane intermediate is formed directly. Reacting the carbanion of the 1,3,2-dioxaphospholane (IV) with benzophenone at 0°C, resulted in a high field ^{31}P-NMR signal at $\delta = +34$ ppm together with the ^{31}P-signals of the carbanion of IV (**5**) and the product phosphate (**8**):



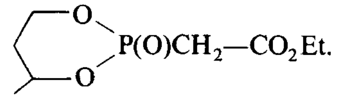
The high-field signal at $\delta = +34$ ppm was attributed to the pentacoordinated intermediate (**6**). No signal due to the oxy-anion (**7**) was reported.

It was hoped that a kinetic study of the Horner-reaction with varying substituents in the phosphonate and aldehyde might give a better understanding of the influence of electronic and steric effects in this useful reaction type. The present paper reports the reaction between para- and meta-substituted benzaldehydes and the following five phosphonates (I–V) where the corresponding phosphoryl stabilized carbanions are generated by sodium ethoxide in ethanol:

(I) $(EtO)_2P(O)CH_2—CO_2Et$,
(II) $(EtO)_2P(O)CH_2—C{\equiv}N$,
(III) $(EtO)_2P(O)CH_2C_6H_4NO_2$, (p)

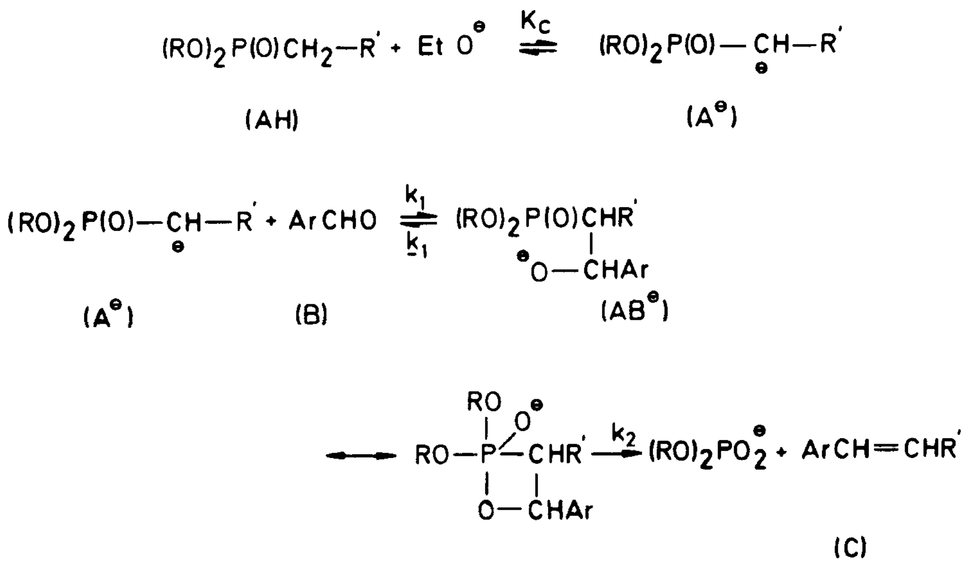
(IV)

(V)



RESULTS AND DISCUSSION

The reaction of the phosphonates, (I–V), with benzaldehyde are very fast reactions when carried out under synthetic conditions where the carbanion is generated with NaH in aprotic solvents such as THF, and the aldehyde added at room temperatures. Excellent yields are then obtained within few minutes, or even seconds.[6] But the high reactivity of phosphonates (I–V) in aprotic medium prevented a kinetic study with the spectroscopical method used in this study. In addition, the low solubility of the sodium dialkylphosphates in aprotic solvents excludes direct monitoring of the reacting mixture with a spectroscopic technique. Using very low concentration of the extremely reactive phosphonate carbanions might lead to serious errors due to uncontrolled hydrolysis or oxidation of the carbanions. However, when the carbanions are generated in equilibrium with its corresponding phosphonate in ethanolic sodium ethoxide, the reactions can be followed spectrophotometrically by conventional techniques. The reaction sequences are as follows (Scheme 2):



SCHEME 2

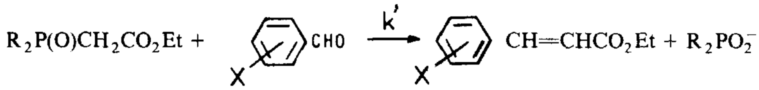
The rate can be conveniently followed under pseudo 1. order reaction conditions. The rate expression for the production of olefin is given by eq. (a), when the intermediates (A^-) and (AB^-) in Scheme 2 are treated according to steady state approximations:[27]

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

K_c is the concentration equilibrium constant for the first acid-base equilibrium given by K_a/K_{EtOH} where $K_{EtOH} = 10^{-18.9}$ is the autoprotolysis constant of ethanol,[28] and K_a is the dissociation constant of the phosphonate (AH). The pK_a-values[26] of phosphonates (I–V) are listed in Table II.

TABLE I

Rate constants for the reaction (at 20.0°C)



		$k' \times 10^{-2}$ [l mole^{-1} s^{-1}]		$\log(k_x/k_0)$	
x	σ_x^{29}	I	IV	I	IV
p-NO$_2$	0.78	38.6	804.0	1.51	1.40
m-NO$_2$	0.71	26.6	790.0	1.35	1.39
m-Cl	0.40	9.7	204.0	0.91	0.80
p-Cl	0.23	4.0	103.0	0.53	0.51
m-MeO	0.10	1.42	33.6	0.08	0.02
H	0.00	1.18	32.0	0.0	0.00
m-Me	−0.07	1.06	22.7	−0.05	−0.15
p-Me	−0.17	0.51	12.0	−0.36	−0.43
		Reaction constants, ρ:	1.95	1.96	
		Correlation coefficients, r:	0.993	0.993	

TABLE II

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

$$\underset{\text{I–V}}{(RO)_2P(O)CH_2R'} + PhCHO \xrightarrow{k'} PhCH{=}CHR'$$

Phosphonate	$k' \times 10^{-2}$ [l mole^{-1} s^{-1}]^a	pK_a
I	1.18	19.75
II	5.80	18.35
III	0.27^b	19.70
IV	32.0	19.90
V	6.17	19.95

[a] k' calculated from eq. 1, with $K_c = K_a/K_{EtOH}$.

[b] This value for the rate constant is for the reaction with p-nitro benzaldehyde.

When the concentrations of the reactants are varied, it was found that the reaction was kinetically overall third order, first order with respect to phosphonate, ethoxide, and aldehyde.

Figure 1 shows the 1. order rate plot of the reaction between phosphonate (II) and benzaldehyde as function of ethoxide concentration.

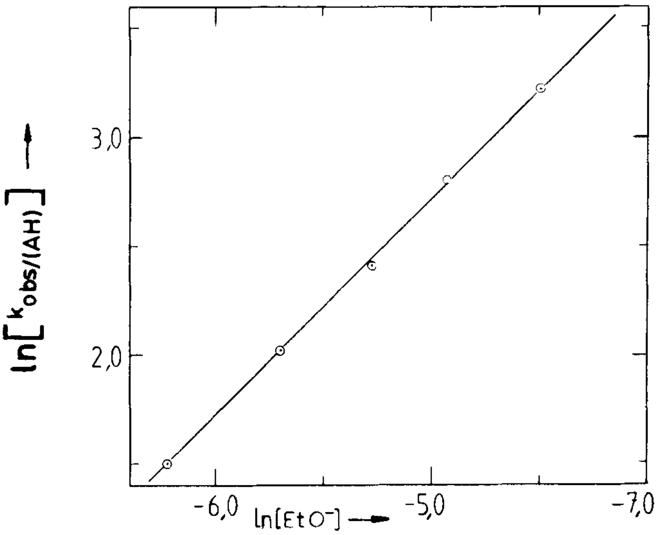


FIGURE 1 Rate of the reaction between II and benzaldehyde at 20.0°C as function of ethoxide concentration.

When the decrease in UV-absorption of aldehyde, and the corresponding increase in olefin absorption are recorded simultaneously (Fig. 2), the rate constants for production of olefin and consumption of aldehyde, under exactly the same conditions, are obtained. Within experimental errors (±3–4%), the rate of production of olefin is always equal to the rate of consumption of aldehyde.

Rate constants for the reactions of phosphonates (I) and (IV) with various substituted benzaldehydes at 20.0°C are recorded in Table I. The rate constants gave excellent Hammet plots[29] (correlation coeff. > 0.99) with the σ-values listed. As the positive sign of the reaction constant, ρ, indicates, the reaction is accelerated by electron withdrawing substituents in *p*- and *m*-positions in the aromatic aldehydes. The results are in accordance with a rate-determining step between the phosphoryl stabilized carbanion and the carbonyl carbon in the aldehyde. (k_1 in Scheme 2). The calculated reaction constant, ρ, in the Horner-reaction is considerably lower than the constant of the analogous Wittig-reaction of ester-stabilized ylides, where ρ is in the range 2.7–3.0.[12–15] The difference is attributed to the much greater nucleophilicity of the phosphoryl stabilized carbanions when compared to the corresponding ylides, producing an earlier transition state in the Horner-reaction. This is also supported by Bergelsons[30] observation that the reaction constant of the highly reactive *n*-

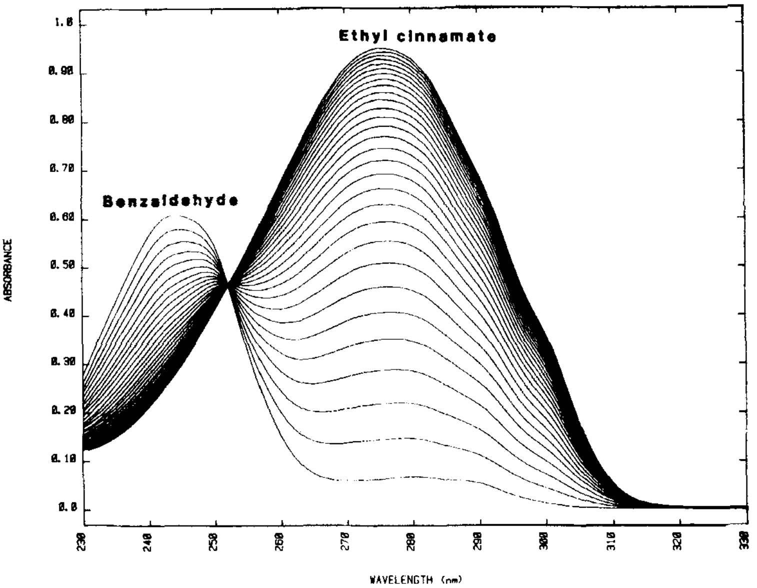


FIGURE 2 UV-spectra of the reaction between I and benzaldehyde, scanned every 80 s. Calculated pseudo 1. order rate constants for consumption of benzaldehyde, $k_{obs} = 1.202 \times 10^{-3}\ s^{-1}$, and for production of ethyl cinnamate, $k_{obs} = 1.230 \times 10^{-3}\ s^{-1}$.

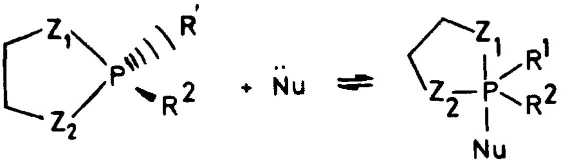
propylidene triphenyl phosphorane with various benzaldehydes is approximately +1.0.

From the close ρ-values for the reactions of phosphonates (I) and (IV), it seems reasonable to assume a very similar transition state for the rate-determining step in the two reactions,[31] i.e. the five-membered phospholane ring does not influence upon the electronic character of the phosphonate anion.

In Table II are recorded the rate constants, k' (see eq. (a)), for the reactions of phosphonates (I–V) with benzaldehyde at 20.0°C, together with the pK_a-values of the starting phosphonates. The reactivity order of the phosphonates (I–III) towards aldehydes ($—C{\equiv}N > CO_2Et > pNO_2C_6H_4$) corresponds to the order of reactivity in similar condensation reactions of stabilized carbanions with benzaldehyde (e.g. the Knoevenagel-reaction[32,33]). It seems reasonable to assume that steric as well as electronic effects contribute to the order of reactivity. Phosphonate (II) has its negative charge largely localized on the α-carbon[34] and reacts faster with the electrophilic carbonyl carbon (charge-control) than (I) and (III) where the negative charge is mainly delocalized on oxygen.[35]

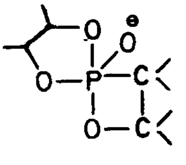
The most striking effect is the large rate increase from the acyclic phosphonate (I) to the five-membered cyclic phosphonate (IV). A rate-determining nucleophilic attack of the phosphonate carbanion on the carbonyl carbon ought to give similar steric and electronic effects in the acyclic and cyclic phosphonates as also the ρ-values indicate. The nearly identical pK_a-values of (I) and (IV) point also to similar electronic effects in the two phosphonates. Further evidence in the same direction comes from the ^{13}C-NMR-spectra of (I) and (IV) and their corresponding carbanions.[36]

Many five-membered cyclic phosphorus compounds containing tetrahedral phosphorus (e.g. phosphates, phosphonium salts, phosphoranes) are found to react faster than their acyclic analogues in reactions leading to pentacoordinated intermediates. The effects are attributed[37-40] mainly to release of ring strain upon passing from tetrahedral (**9**) to the trigonal-bipyramidal structure in the intermediate in which the five-membered ring occupies an apical-equatorial structure (**10**).



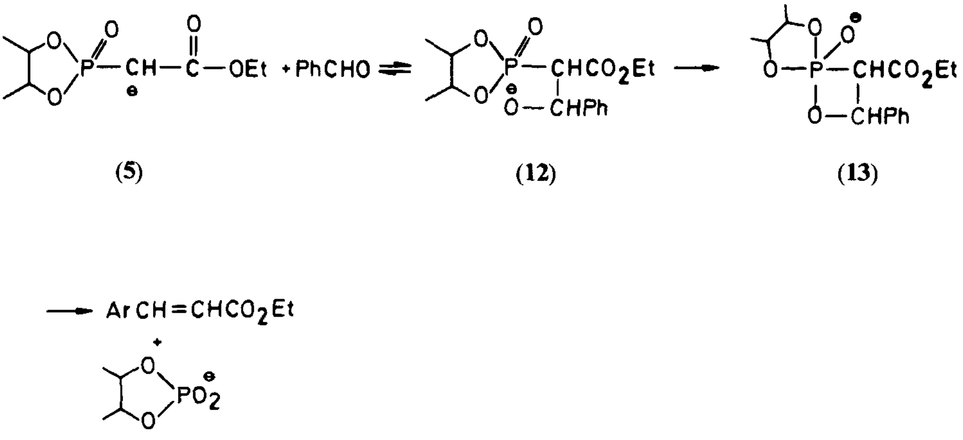
(**9**) (**10**)

In the reaction of (IV), the formation of the spiro-phosphorane (**11**) is thought to be very favourable since both the five- and four-membered rings prefer the apical equatorial position over the diequatorial one, while the oxy-anion prefers the equatorial position over the apical one.[40,41]



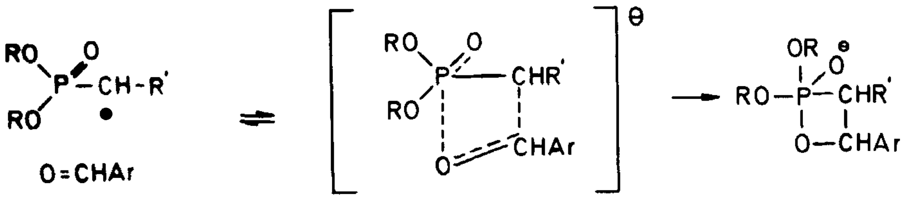
(**11**)

Phosphonate (IV) has previously been shown to give a much higher proportion of *cis*-olefin in the reaction with benzaldehyde than (I), (~ 60% and ~ 2% respectively). This has been attributed[23,42] to an increase in the rate of attack of the oxyanion (**12**) on phosphorus leading to the pentacoordinated intermediate (**13**).



But the very similar reaction constants, ρ, of the reactions of (I) and (IV) with substituted benzaldehydes, and the large rate increase, do not support a rate-determining formation of a β-oxy-anion intermediate (**12**) before the ring closure to (**13**) takes place. Similar rate accelerations, in passing from acyclic to five-membered cyclic phosphoranes, have been observed in the Wittig-reaction,[16] which is believed to lead directly to pentacoordinated intermediates.[43] From the known stabilities of oxyphosphoranes, the proposed intermediates in the present reactions ought to be formed faster than the intermediates in the Wittig reaction, since the less electronegative C-atoms of the latter are forced into apical position, thus having a destabilizing effect on the phosphorane intermediate.[40]

The present data support the conclusion that the P—O bond is also being formed in the rate-determining step, and that the reaction leads directly to the pentacoordinated intermediate.



EXPERIMENTAL

Materials. The phosphonates were synthesized by the Michaelis–Arbuzov reaction from the appropriate phosphites and halides.[19]

2-Carbethoxymethyl-diethylphosphonate, (*I*). Bp 129°C (5 mm), n_D^{22} = 1.4306, Reported[20] Bp. 109–109.5°C (0.8 mm), n_D^{18} = 1.4316.

2-Cyanomethyl-diethylphosphonate, (*II*). Bp. 142–3°C (6–7 mm), n_D^{22} = 1.4316, Reported[21] Bp. 126–7 (2 mm), n_D^{20} = 1.4310.

4-Nitrobenzyl-diethylphosphonate, (*III*). Bp. 142°C (0.05 mm), n_D^{22} = 1.5238, Reported[22] Bp. 148–53°C (0.1 mm), n_D^{25} = 1.5220.

2-Carbethoxymethyl-4,5-dimethyl-2-oxo-1,3,2-dioxaphospholane (*IV*). 4,5-dimethyl-2-methoxy-1,3,2-dioxaphospholane, prepared by transesterification of trimethylphosphite with 2,3-butanediol (meso + dl), was added to ethylbromoacetate at 120°C. Subsequent heating of the reaction mixture to 60°C, yielded (IV) (meso + dl). Bp. 138°C (0.05 mm), n_D^{22} = 1.4517, Reported[23] Bp. 135°C (0.3 mm), n_D^{20} = 1.4550. No significant rate effects were observed when the reactions of the five-membered phosphonate (IV) were carried out using a five-membered phosphonate very rich in either dl—or one of the meso-isomers. Nor does the isomer composition in (IV) affect the ratio of geometrical isomers in the products, as observed by Breuer *et al.*[23]

2-Carbethoxymethyl-4-dimethyl-2-oxo-1,3,2-dioxaphosphorinane, (*V*). 4-methyl-2-methoxy-1,3,2-dioxaphosphorinane (prepared by transesterification of trimethylphosphite and 1,3-butanediol) was slowly added to ethyl-bromoacetate at 110–120°C. Keeping the mixture at 150°C for 2 hours, gave (V). After three repeated fractionations, the purity was better than 99.5% on GLC. Bp. 136°C (0.01 mm), n_D^{22} = 1.4610.

Anhydrous ethanol was obtained by the magnesium-alcoholate method.

Sodium ethoxide in ethanol was prepared by dissolving fresh-cut sodium-metal in anhydrous ethanol under argon atmosphere, and standardized against hydrochloric acid.

The commercial aldehydes were distilled or recrystallized prior to the kinetic measurements.

The reactant solutions were always prepared just before the kinetic runs.

Kinetic measurements. The rates of reaction of the phosphonates with the substituted benzaldehydes were determined by following the ultraviolet absorption spectra of the olefins or the reacting aldehydes. The reactions were performed under pseudo 1. order conditions, usually with large excess of base and phosphonate over aldehyde. The pseudo 1. order rate constants were determined from the slope of a plot of $\ln[A_{t+\Delta} - A_t]$ against time, where A_t is the absorbance at time t and Δ is a constant time interval between 2 and 3 half-lives of the reaction. The reactions were always followed to at least 5 half-lives.

The reaction was started by adding a small volume of an aldehyde solution ($\sim 10\ \mu l$) to a septum-capped UV-cell (1 cm) containing the freshly prepared solution of the sodium ethoxide and phosphonate under N_2-atmosphere. The concentration of the aldehydes were in the region $3\text{–}5 \times 10^{-5}$ whereas the concentrations of base and phosphonates were approximately 100–250 fold in excess of the aldehyde concentration.

The kinetic measurements were performed on a Hewlett-Packard 8450A UV/VIS Spectrophotometer, equipped with a HP 82901M Flexible Disc Drive and a HP 9872B Plotter.

pK_a-determinations. The pK_a-values of the phosphonates (I–V) have been established in a stepwise manner as described by Dolman and Stewart.[24] The pK_a-values reported are relative to that of diethylmalonate (17.59) measured in ethanolic sodium ethoxide at 25°C. (Reported[25] 17.56). Ionization ratios were determined spectrophotometrically in mixtures of dimethylsulphoxide (DMSO) and ethanol with constant concentration of sodium ethoxide (0.01 M).

The reported pK_a-values are thus referred to pure ethanol as standard state. Since the absorption maximum of the carbanions derived from phosphonate (I) and (III–V) were obscured by the solvent, measurements were performed on wavelengths where the solvent did not interfere. The extinction coefficients of the anions were calculated from the absorbance data in 95 mole% DMSO in ethanol and with 0.01 M sodium ethoxide. In this strongly basic medium the phosphonates are almost completely ionized. Within experimental errors, the ionization ratios remained constant when absorption data at different wavelengths were used in the calculations for a particular compound. This indicates that there are no serious solvent effects on the anion spectra in the various DMSO/ethanol-mixtures.

The experimental errors of the calculated pK_a-values of the phosphonates (I–V) are within ± 0.10 units. Further experimental details are reported in ref. 26.

ACKNOWLEDGEMENT

One of us (R. O. L.), is indebted to the Norwegian Research Council for Science and the Humanities for a Fellowship.

REFERENCES

1. L. Horner, H. Hoffmann and H. G. Wippel, *Chem. Ber.*, **91**, 61 (1958).
2. W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).
3. A. V. Dombrovskii and V. A. Dombrovskii, *Russ. Chem. Rev.*, **35**, 733 (1966).
4. A. W. Johnson, "Ylid Chemistry", Academic Press, New York, 1966, Ch. 5.
5. I. Boutagy and R. Thomas, *Chem. Rev.*, **75**, 87 (1974).
6. W. S. Wadsworth, Jr., *Org. React.*, **25**, 73 (1978).
7. B. J. Walker in "Organophosphorus reagents in organic synthesis", (ed. by J. I. Cadogan), Academic Press, London, 1979, Ch. 3.
8. G. Durrant and J. K. Sutherland, *J. Chem. Soc., Perkin I*, 2582 (1972).
9. D. Danion and R. Carrie, *Tetrahedron*, **28**, 4223 (1972).
10. B. Deschamps, G. Lefebre and J. Seyden-Penne, *Tetrahedron*, **28**, 4209 (1972).
11. T. Bottin-Strzalko, *Tetrahedron*, **29**, 4199 (1973).
12. A. J. Speziale and D. E. Bissing, *J. Amer. Chem. Soc.*, **85**, 3878 (1963).
13. C. Rüchardt, P. Panse and S. Eichler, *Chem. Ber.*, **100**, 1144 (1967).
14. S. Fliszar, R. F. Hudson and B. Salvadori, *Helv. Chim. Acta*, **46**, 1580 (1963).
15. B. Giese, J. Schoch and C. Rüchardt, *Chem. Ber.*, **111**, 1395 (1978).
16. P. Frøyen, *Acta Chem. Scand.*, **26**, 2163 (1972).
17. G. Aksnes and F. Y. Khalil, *Phosphorus*, **2**, 105 (1972); **3**, 37, 79, 109 (1973).
18. E. Breuer, S. Zbaida and E. Segall, *Tetrahedron Lett.*, 2203 (1979).
19. K. Sasse in "Methoden der Organischer Chemie" (Houben-Weyl) (ed. E. Müller), Vol. 12, part 1, G. Thieme, Stuttgart, 1964.

20. J. Wolinsky and K. L. Ericson, *J. Org. Chem.*, **30**, 2208 (1965).
21. A. N. Pudovik and N. M. Lebedeva, *Zh. Obshch. Khim.*, **25**, 2235 (1955).
22. F. Kagan, R. D. Birkenmeyer and R. E. Strube, *J. Amer. Chem. Soc.*, **81**, 3026 (1959).
23. E. Breuer and D. M. Bannett, *Tetrahedron*, **34**, 997 (1978).
24. D. Dolman and R. Stewart, *Can. J. Chem.*, **45**, 911 (1967).
25. R. Pearson, *J. Amer. Chem. Soc.*, **71**, 2212 (1949).
26. R. O. Larsen, to be published.
27. See for example A. A. Frost and R. G. Pearson, "Kinetics and Mechanism", 2nd. ed., John Wiley, 1961.
28. G. Briere, B. Crochon and N. Felici, *Compt. Rend.*, **254**, 4458 (1962).
29. See for example R. Fuchs and E. S. Lewis in "Techniques of organic chemistry", Vol. 6, ch. 14, Wiley Interscience, 1974.
30. L. D. Bergelson, L. I. Barsukov and M. M. Shemyakin, *J. Gen. Chem. USSR.*, **82**, 2396 (1960).
31. C. D. Johnson, "The Hammet Equation", Cambridge University Press, 1973.
32. G. Jones, *Org. React.*, **15**, 204 (1967).
33. S. Patai, J. Zabicky and Y. Israeli, *J. Chem. Soc.*, 2038 (1960) and refs. cited.
34. R. P. Bell, "The Proton in Chemistry", 2nd ed., Ch. 10, Chapman and Hall, London, 1973.
35. M. Cossentini, B. Deschamps, N. T. Ahu and J. Seyden-Penne, *Tetrahedron*, **33**, 409 (1977) and refs. cited.
36. R. O. Larsen to be published.
37. F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).
38. G. Aksnes and K. Bergesen, *Acta Chem. Scand.*, **20**, 2508 (1966).
39. R. F. Hudson and C. Brown, *Accounts Chem. Res.*, **5**, 204 (1972).
40. P. Gillespie, F. Ramirey, I. Ugi and D. Marquarding, *Angew. Chem., Internat. ed.*, **12**, 91 (1973).
41. S. Trippett, *Pure Appl. Chem.*, **40**, 595 (1974).
42. E. Breuer and D. Bannet, *Tetr. Lett.*, 1141 (1977).
43. H. J. Bestmann, *Pure Appl. Chem.*, **51**, 515 (1979); **52**, 771 (1980).