THE KINETICS OF WITTIG'S REACTION OF α-ETHOXYCARBONYL-ALKYLIDENEPHOSPHORANES WITH AROMATIC ALDEHYDES

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The kinetics of Wittig's reaction of *p*- and *m*-substituted benzaldehydes with α-ethoxycarbonylalkylidenephosphoranes $(C_6H_5)_3P{=}C(R)COOC_2H_5$ ($R = CH_3$, C_2H_5, n-C_3H_7) was studied and correlation analysis applied to the evaluation of the effect of substituents in benzaldehydes and of alkylation at the C_α atom in the phosphoranes on the reaction rate. The conclusions show that the effect of alkyl residues in the phosphoranes of this type is not determined solely by the inductive effect and by steric reasons. The NMR and IR spectra of the α-ethoxycarbonylalkylidenephosphoranes were recorded and it was found that the splitting of proton signals due to spin-spin interaction with the phosphorus atom is transferred all the way to the protons on the carbon atom which is bound to the α-carbanion.

In connection with the preparation of branched arylaliphatic carboxylic acids with the potential anti-inflammatory effect[1-3] we set out to synthesize α-alkylcinnamic acids. The preparation and the biological properties of these compounds will be described elsewhere. For this purpose we made use of Wittig's reaction[4,5] of substituted benzaldehydes with α-ethoxycarbonylalkylidenephosphoranes and obtained a series of ethyl esters of cinnamic acids substituted in the α-position with respect to the carboxyl with methyl, ethyl and n-propyl groups. The required phosphoranes *II* were prepared by dehydrohalogenation of the corresponding phosphonium salts *I* (equation *A*) which had been obtained by a reaction of triphenylphosphine with ethyl esters of α-bromopropionic, α-bromo-n-butyric and α-bromo-n-valeric acids.

Determination of NMR spectra of the α-ethoxycarbonylalkylidenephosphoranes (Table I) revealed a splitting of the signals belonging to the protons at the C atom attached to the α-carbanion, due to a spin-spin interaction with the phosphorus atom. The splitting is marked with phosphoranes *IIb* and *IIc** while with phosphorane *IId* it is covered by the signals of protons of the two methylene groups in the n-propyl residue. This result is in agreement with the NMR spectrum of α-methoxycarbonylethylidenephosphorane reported by Bestmann and coworkers[6,7]. Protons at the other C-atoms are not affected by this interaction at the experimental temperature. Protons in the ethyl group of the ester are characterized by normal signals, *i.e.* a quadruplet and a triplet, and only in the case of the α-n-propyl derivative *IId* are they hard to distinguish.

* This splitting was also observed in phosphorane *II* ($R = CH_2COO{-}C_2H_5$) and α-acetyl-β-ethoxycarbonylethylidenephosphorane.

According to Bestmann and coworkers[6], the esterphosphoranes *II* probably exist as two rotamers with *cis* and *trans* configurations in the sense of formulation *II-cis* and *II-trans* (Eq. (*B*)). At low temperatures the two isomers are characterized by different signals which merge with increasing temperature. In the case of *IId* the merging temperature is close to the experimental one.

In connection with the synthesis of esters of cinnamic acids we took up the kinetics of Wittig's reaction of the above phosphoranes *II*, in particular the effect of alkylation on their reactivity. We examined the kinetics of reaction of phosphorane *IIc* with substituted benzaldehydes (Table II) assuming that the reaction follows the mechanism proposed for the resonance-stabilized phosphoranes[8,9]. The reaction proceeds in two steps; in the first step a slow reversible reaction gives rise to a mixture of diastereoisomeric betaines of *threo-* and *erythro*-configuration which, in the second step, are decomposed by a *cis*-elimination mechanism to a mixture of *cis* and *trans* olefinic compounds and triphenylphosphine oxide (Eq. (*C*)). The reaction is second-order and, on the assumption of a steady state, it is kinetically determined by the

$$(C_6H_5)_3P + RCH(Br)COOC_2H_5 \rightarrow \underset{Ia-d}{(C_6H_5)_3P^{(+)}-CH(R)COOC_2H_5Br^{(-)}} \rightarrow$$

$$\rightarrow \underset{IIa-d}{(C_6H_5)_3P{=}C(R)COOC_2H_5} \qquad (A)$$

R: *a*) H; *b*) CH_3; *c*) C_2H_5; *d*) n C_3H_7,

II-cis *II-trans* *(B)*

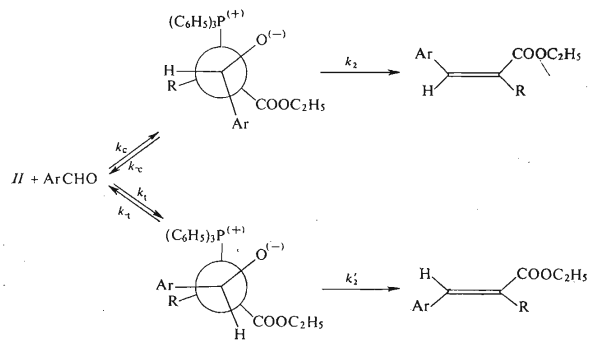

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TABLE I

Properties of Phosphoranes $(C_6H_5)_3P{=}C(R^1)COOR^2$

bs broad singlet, d doublet, t triplet, q quadruplet.

R^1 R^2	pK_b	δ, p.p.m. a	b	c	d	e	ν, cm^{-1}	$CHCl_3$ KBr	
H^a	4·80	2·85 bs	3·96 q	1·02 t	—	—	1 110	1 441	1 615
$CH_2^bCH_3^c$			J = 7·0 Hz	J = 7·0 Hz			1 112	1 440	1 610
CH_3^a	3·80	1·60 d	3·84 q	0·67 t	—	—	1 111	1 445	1 607
$CH_2^bCH_3^c$		J = 14·0 Hz	J = 7·0 Hz	J = 7·0 Hz			1 098	1 440	1 630
$CH_3^aCH_3^d$	4·20	1·80 q; 2·14 q	3·80 q	0·65 t	0·86 t	—	1 113	1 443	1 606
$CH_2^bCH_3^c$		J = 7·0 Hz	J = 7·0 Hz	J = 7·0 Hz	J = 7·0 Hz		1 111	1 443	1 620
$CH_2^aCH_2^dCH_3^c$	4·25	1·0—2·25 m*	3·70 q**	0·44 t**	1·0—2·25 m*	0·65 t	1 108	1 443	1 605
$CH_2^bCH_3^c$						J = 6·0 Hz	1 110	1 445	1 624

*The signals of protons a and d overlap; **a poorly distinguishable quadruplet and triplet.

rate of formation of betaines as was demonstrated experimentally for this type of phosphoranes[8,10,11].

It follows from the reaction scheme that we are dealing here with a system of two parallel reactions. In this case, the interpretation of the reaction constant ϱ in relation to the experimental rate constants is possible only under certain conditions[12]. Both parallel reactions are characterized in the first step by two rate constants k_t, k_c, the changes of which with the substitution in the aldehyde are illustrated by two reaction constants ϱ_1 and ϱ_2. Under the assumption that

$$\varrho_1 \approx \varrho_2 = \varrho \qquad (1)$$

it will hold that

$$\log (k_t + k_c) = \varrho \,.\, \sigma + \log (k_t^0 + k_c^0) \,. \qquad (2)$$

We assume that this postulate is valid since both transition states, *threo* and *erythro*-betaine, are so close that they reflect approximately equally the changes in the substitution of the aldehyde.

To compare the results of Speziale and Bissing[8] in context with the set of reactions of methoxycarbonylmethylenephosphorane the kinetic measurements were done in the same way, *i.e.* in benzene at 25°C in an atmosphere of nitrogen and the reaction course was followed by the decrease in the amount of phosphorane *IIc*. By correlating the rate constants obtained with Hammett's constants of the substituents we could determine the reaction constant ϱ as 2·89 which is practically identical

TABLE II

Kinetics of the Reaction

$$(C_6H_5)_3P{=}C(C_2H_5)COOC_2H_5 + X{-}C_6H_4{-}CHO \rightarrow$$
$$\rightarrow X{-}C_6H_4{-}CH{=}C(C_2H_5)COOC_2H_5$$

X	σ^a	$k \,.\, 10^5$	$\log k_X/k_H$	$\log k$	$\log k_{calc}$
p-NO_2	0·78	4090·0	2·21	−1·385	−1·364
m-Cl	0·38	293·2	1·06	−2·530	−2·548
p-Cl	0·23	86·0	0·53	−3·058	−2·953
p-F	0·06	71·6	0·45	−3·250	−3·444
H	0	25·3	0	−3·600	−3·617
p-$(CH_3)_2CH$	−0·15	10·0	−0·40	−4·000	−4·050
p-CH_3	−0·17	6·2	−0·61	−4·222	−4·108
p-CH_3O	−0·27	3·7	−1·14	−4·435	−4·397

[a] The σ constants from ref.[13].

with the reaction constant for methoxycarbonylmethylenephosphorane* (Fig. 1). It can thus be said that the mechanism of reaction of phosphoranes *II* with aldehydes is not affected by alkylation at the α-carbanion.

TABLE III

Kinetics of the Reaction

$$(C_6H_5)_3P{=}C(R^1)COOR^2 + C_6H_5{-}CHO \rightarrow C_6H_5{-}CH{=}(R^1)COOR^2$$

R^2	R^1	$k \cdot 10^5$	$\log k$	σ^*	E_S[a]
C_2H_5	H	172·4	−2·76	0·49[b]	1·24
	CH_3	1061·0	−1·97	0	0
	C_2H_5	25·3	−3·59	−0·10[b]	−0·07
	n-C_3H_7	9·75	−4·01	−0·115[b]	−0·36
CH_3[c]	H	96·0	−3·02	0·49	1·24
	Cl	57·5	−3·24	2·9[d]	0·18
	Br	18·5	−3·73	2·8[d]	0·01

[a]The steric constants from ref.[17]; [b]the polar constants from ref.[18] and [d]from ref.[19]; [c]kinetic data from ref.[8].

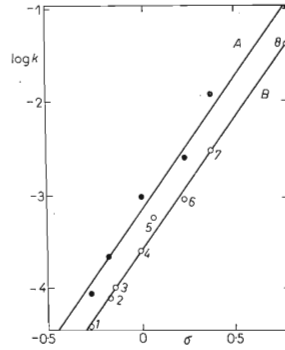

FIG. 1

Dependence of $\log k = \varrho \cdot \sigma + \log k_0$ for the Reaction of $(C_6H_5)_3P{=}C(R^1) \cdot COOR^2$ with Substituted Benzaldehydes

A (values from ref.[8]): $R^1{=}H$, $R^2{=}CH_3$ (ϱ 2·96; *r* 0·995) *B*: $R^1 = R^2 = C_2H_5$ (ϱ 2·89; *r* 0·997); *1* *p*-CH_3O, *2* *p*-CH_3, *3* *p*-$(CH_3)_2CH$, *4* H, *5* *p*-F, *6* *p*-Cl, *7* *m*-Cl, *8* *p*-NO_2.

* Speziale and Bissing[8] report a value of ϱ equal to 2·7. By recalculation of the data using the method of Jaffé[13] we reached a value of 2·96. This is also close to the value in ref.[14] (2·9) for the reaction of phosphorane *IIa* with substituted benzaldehydes in acetonitrile.

Fig. 1 also shows that the substitution of the α-H atom with ethyl decreases the reactivity of the esterphosphorane *II*. The effect of alkylation on reactivity was confirmed by determining the reaction rates of phosphorane *IIa* and of its α-alkyl derivatives *IIb,c,d* with benzaldehyde. The high reactivity of the α-methyl derivative *IIb* is rather surprising (Table III). The exceptional effect of methyl on reactivity was accounted for in an analysis of the effect of alkyl on the α-carbanion of the esterphosphoranes *II*. We assumed that the substituents can affect the electron density at the C_α atom by an inductive, primary and secondary steric, or by other types of effect. The inductive effect of the alkyl increases the electron density at the α-carbanion and thus the nucleophilic character of the phosphorane. The primary steric effect decreases the reactivity with increasing size of the alkyl and, to some extent, accounts for the drop of reactivity of phosphoranes *II* in the series $CH_3 > > C_2H_5 > n\text{-}C_3H_7$. The inaccuracy of this explanation is exhibited by a comparison of the reactivity of phosphoranes *IIb* and *IIc* with the pair of halogenated phosphoranes *II* (R = Cl or Br)[8]. In both pairs there are close differences in the induction effects (expressed by σ^*) and in the effective volumes (expressed by E_S). Nevertheless, the drop of the reaction rate of phosphorane *II* (R = Br) as compared with *II* (R = Cl) is approximately three-fold while in the case of *IIc* and *IIb* the difference is more than forty-fold. It is thus unlikely that the primary steric effect alone would be responsible for the substantial drop of reactivity of the phosphoranes *IIc* and *IId*. The secondary steric effect which brings about the decrease of the complanarity of the resonance system P=C—C=O, increases the nucleophilic character of phosphoranes *II* in the same sequence as the induction effect.* Its possible role would thus increase the discrepancy between the reactivity of phosphoranes *II* and the effect of the primary steric and the induction effect. One can thus assume with some justification that the substituents affect the α-carbanion of the phosphoranes by another effect which is associated with the number of the C—H bonds proceeding from the C-atom bound to the reactive centre. These bonds have thus apparently a negative effect on the stabilization of the α-carbanion.

To determine the mechanism of this effect,** unless one remains in the realm of speculation, would require an extension of the variety of substituents, above all by secondary or tertiary alkyls. Phosphoranes *II* with such substitution could not be prepared either by alkylation of ethoxycarbonylmethylenephosphorane (*IIa*)

* In this connection it is of interest to observe the X-ray analysis of α-halogeno-β-oxoalkylidenephosphoranes[15] which are sterically more demanding than *II* and still planar arrangement of the P—C—C—O bonds is not markedly affected.

** The decrease of stability can be accounted for, *e.g.*, by overlapping of the sp^3 orbitals of these bonds with the sp^2 orbitals of the α-carbanion. This would decrease the percentage of the *s*-orbital in the orbitals of the α-carbanion and, due to this negative *s*-orbital effect[16], its stability is decreased and reactivity increased. Hybridization of the sp^2 of the α-carbanion was shown in ref.[15] using α-halogeno-β-oxoalkylidenephosphoranes.

using suitable alkylhalogenides, or by a reaction of the α-bromo derivatives of esters of branched fatty acids with triphenylphosphine and subsequent dehydrobromination of the phosphonium salts formed. Further solution of the problem was then transferred to the group of β-oxoalkylidenephosphoranes where the conditions for the preparation of suitably substituted derivatives are more favourable.

EXPERIMENTAL

Methods and Kinetic Measurements

The IR absorption spectra of phosphoranes *II* between 400 and 4000 cm^{-1} were recorded in a 3% solution in chloroform or in a KBr pellet using the Zeiss (Jena) UR-20 spectrophotometer The NMR spectra of phosphoranes *II* were recorded in a Zeiss (Jena) ZKR 60 spectrometer using 6% solutions in deuteriochloroform at room temperature. As internal standard served here hexamethyldisiloxane and the values obtained were compared with tetramethylsilane. The p*K* values of phosphoranes *II* were determined in methanol on a Titrigraph (Radiometer) type SBR 2c. The same apparatus was used for evaluating samples of the reaction mixtures during kinetic measurement. The melting points were determined in a melting block of Boëtius M type and are not corrected.

An approximately 0·125M solution of phosphorane *II* was prepared in benzene and its content was determined potentiometrically in 90% methanol. The solution (50·0 ml, about 6·25 mmol) was added at 25 ± 05°C (Ultrathermostat U 10) all at once to a solution of an equimolar amount of the corresponding aldehyde (freshly distilled) in 12·5 ml benzene in a nitrogen atmosphere. Aliquot portions that were removed at suitable time intervals were poured into excess 0·1M-HCl in 90% methanol and the excess of acid was determined by back titration. Another method was also used[8] when the samples of the reaction mixture were poured into methanol (0°C) and, within 10 min, the content of nonreacted phosphorane was determined. It was found that the values of the reaction rate thus obtained are identical with the value determined by the preceding method. The individual points of the linear relationship $x/a.(a - x)$ on time are subject to an error which indicates the decomposition of the phosphorane in the methanolic solution. This decomposition was demonstrated also by determining the phosphorane content in the methanol solution at 25°C within 12 h. The rate constants were calculated as the slopes of curves relating $x/a.(a - x)$ to time. The reaction constant ϱ, the correlation coefficient r and the values of $\log k_{cal}$ were obtained by the least-squares method[13].

Compounds Used

Triphenylethoxycarbonylmethylenephosphorane (IIa): m.p. 125—127°C (ref.[20,21] gives a m.p. of 116—117°C; 125—127·5°C). *Triphenyl-α-ethoxycarbonylethylidenephosphorane* (IIb): m.p. 165—167°C (ref.[20] gives a m.p. of 156—157°C). *Triphenyl-α-ethoxycarbonylpropylidenephosphorane* (IIc): Ethyl α-bromobutyrate (8·5 g; 44·5 mmol) in 5 ml acetonitrile was added to a solution of 9·80 g (39·0 mmol) triphenylphosphine in 20 ml acetonitrile at 60°C. The mixture was boiled under stirring for 15 h, concentrated *in vacuo* and the oily residue combined with 20 ml ethyl acetate and 5 ml acetonitrile. On cooling to 0°C, the phosphonium salt *Ic* crystallized. This was filtered and washed with a mixture of ethyl acetate and light petroleum (1 : 1). In this way, 11·3 g (63·4%) *Ic* was obtained, this being dissolved in 150 ml water, filtered with charcoal and the filtrate was made alkaline at 20°C with 1M-NaOH to a positive reaction to phenolphthalein. The precipitated product was extracted with 100 ml benzene, the benzene solution was dried

with magnesium sulfate and, after concentration in vacuo, crude *IIc* was obtained. Crystallization from ethyl acetate yielded a product melting at 129—130°C (6·7 g; 70·0%). For $C_{24}H_{25}O_2P$ (362·4) calculated: 76·15% C, 6·39% H, 8·54% P; found: 76·38% C, 6·38% H, 8·72% P.

Triphenyl-α-ethoxycarbonyl-n-butylidenephosphorane (IId): From 13·8 g (55·0 mmol) triphenylphosphine and 12·4 g (64·0 mmol) ethyl α-bromo-n-valerate, a crude phosphonium salt *Id* was obtained in a 59·6% yield and treated as in the preceding case. The phosphorane *IId*, melting at 96—96·5°C (from ethyl acetate) was obtained in a yield of 58·3%. For $C_{25}H_{27}O_2P$ (390·4) calculated: 76·95% C, 6·97% H, 7·92% P; found: 77·16% C, 7·14% H, 7·83% P.

The elementary analyses were carried out in the microanalytical department of this institute (headed by Dr J. Körbl).

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