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KINETICS AND LINEAR FREE ENERGY RELATIONSHIP OF WITTIG REACTION BETWEEN SUBSTITUTED BENZALDEHYDES AND SUBSTITUTED BENZYLIDENETRIPHENYLPHOSPHORANE

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Abstract—Kinetics and linear free energy relationship (LFER) of Wittig reaction of ylides of intermediary stability have been investigated. Evidences are presented which indicate that under such cases the reaction follows a second order rate law, first order in phosphorane and aldehyde respectively, and furthermore that electron withdrawing substituents on both benzaldehyde and benzylidenetriphenylphosphorane impose rate enhancement effect upon the reaction. The mechanism of the reaction is discussed on the basis of the experimental findings.

INTRODUCTION

In previous literatures, studies on the mechanism of Wittig reaction was confined to those of stable and unstable ylides[1]. Reports on this kind of reaction of ylides of intermediary stability were seldom. Kinetic studies by previous authors have indicated that, in the absence of lithium halide, the rate determining step is the formation of intermediate, betaines[2]. However, the kinetic behavior for the intermediately stable ylide in the presence of LiBr is somewhat different from those for the stable and unstable ones[3].

Since ylides of intermediary stability are frequently employed in organic syntheses to react with aldehydes, it is, therefore, of practical significance to study the mechanism of this kind of reaction under the said conditions. With such a view in mind, we have devised the present approach by selecting several substituted benzaldehydes to react with some substituted phosphoranes in the presence of LiBr, so as to find out the response on the kinetic behavior and the LFER caused by the variation of the substituents on both components, attempting to explore some significant insight concerning the specific kinetic detail under such reaction conditions.

RESULTS AND DISCUSSION

Reactions between Substituted Benzaldehydes and Ylides.

Firstly, the kinetics of the reactions between a series of substituted benzaldehydes with a ylide, p-methylbenzylidenetriphenylphosphorane, was examined. Starting with equivalent amounts of the aldehyde and ylide, reactions were conducted in methanol in the presence of LiBr. Titration with standardized HCl–ethanol was employed to follow the change of the concentration of the ylide remained in the reaction system. Treatment of the kinetic data indicates that the reaction is second order, first order with respect to phosphorane and aldehyde respectively. Using least square method, the relationship between the reciprocal of the concentration (1/C) and time (t) to give a regression equation, $1/C = a + bt$ with a correlation coefficient, r where b corresponds to rate constant k that was experimentally measured at 25°C, 34°C and 43°C. The activation parameters were calculated accordingly. The results are listed in Table 1.

Method of titration was again used in conjuntion with high performance liquid chromatography

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TABLE 1. Kinetic Parameters of the Reactions Between Substituted Benzaldehydes and p-Methylbenzylidenetriphenylphosphorane

Substituents	Temperature	$k \cdot 10^{2a}$ Mole · min^{-1}	E_a Kcal/Mole	$\Delta g^{\neq}$ (e. u.)
H	25.0	3.57	16.1	-13.1
	34.5	9.25		
	43.5	17.40		
p-CH_3	25.0	2.20	17.0	-11.2
	34.5	5.67		
	43.5	11.70		
p-CH_3O	25.0	0.96	15.7	-16.4
	34.5	2.79		
	43.5	4.47		
p-Cl	25.0	10.80		
m-Br	25.0	21.50		
m-NO_2	25.0	52.10		

*k is reproducible within a range of relative error less than ± 0.04.

to monitor the concentrations of ylides and aldehydes and thereby derived the rates. Data obtained from both methods are found to check fairly well with one another. The reaction products were isolated and identified by recrystallisation, melting point determination and elementary analysis.

Figure 1. shows the plot of 1/C versus t for the reaction of the ylide and substituted benzaldehydes.

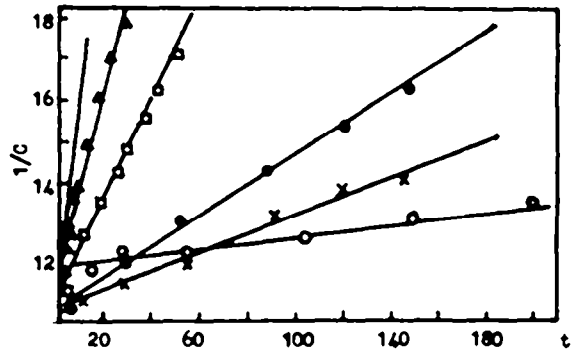


Fig 1. 1/C–t relationship of the reaction of substituted benzaldehydes and p-methylbenzylidenetriphenylphosphorane (25°C). o:P-CH_3O (r=0.997); x:p-CH_3(r=0.998); •:H(r=0.997); □:p-Cl(r=0.997); ▲:m-Br(r=0.996); △:m-NO_2(r=0.999).

Satisfactory linear relationship between these two factors shows evidently that the reaction is second order and electron withdrawing substituents impose rate enhancement of the reaction is demonstrated by steeper slopes of their corresponding lines.

Inspection of the substituent effect by regression with the classical substituent constants and log k gives the following regressive equation:

$$\log k = 1.75\sigma - 1.43 \qquad (1)$$

with a correlation coefficient, r = 0.990, k being the corresponding rate constant at 25°C.

Plot of log k versus t shows good linear relationship as depicted in Figure 2.

In accordance with the field-mesomerism-mesomeric field (FMMF) method of Dewar, σ_{im} of a substituent at some position i acting on the functional group on some site m in the conjugated system can be calculated by following equation:[4]

$$\sigma_{im} = F^S R_{im} + M^S q_{im} + M_P^S \sum_{k \neq m} \frac{q_{ik}}{r_{km}}$$

$$R_{im} = 1/r_{in} - 0.9/r_{jn}$$

where F^S, M^S and M_P^S are constants which are taken from literature[4], r_{in}, r_{jn} and etc. are

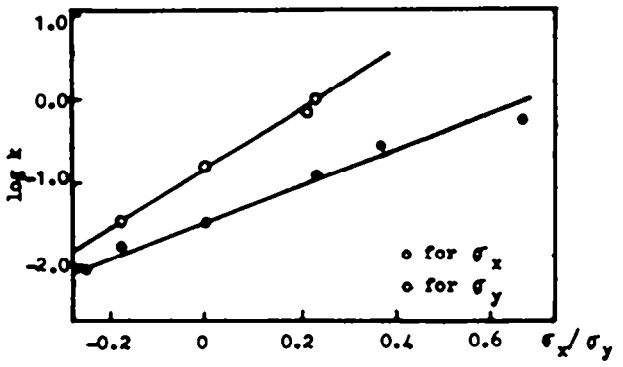


Fig 2. Effect of the variation of substituents on aldehydes and ylides on reaction rate. X and Y represent the substituents on phosphorane and benzaldehyde respectively; σ_x and σ_y, the corresponding substituent constants of X and Y.

distances between the sites indicated wherein and q_{im} and q_{ik} are electron densities at the sites indicated whereon.[4] The corresponding para and meta substituent constants are thus expressed as follows:

$$\sigma_{im}^{(p)} = 0.108F + 0.143M + 0.108M_p$$

$$\sigma_{im}^{(m)} = 0.118F + 0.213M_p$$

The values for some substituents calculated thereby are listed in Table 2.

TABLE 2. Substituent constants calculated by PMMP Method

Substituents	H	p-CH_3	m-Br	p-CH_3O	m-NO_2
σ_{im}	0.331	-0.178	0.516	-0.244	0.926

Regression with the constants thus obtained and the log k, at 25°C gives the following equation:

$$\log k = 1.43\,\sigma_{im} + 1.50 \qquad (2)$$

with a correlation coefficient, r = 0.982

From equations (1) and (2), it can be seen that the reaction rate increases prominently with increasing the electron withdrawing power of the substituents, since in both methods of treatment, the reaction constants are positive and greater than unity, i.e. $\rho > 1$.

The activation entropies obtained thereby are likewise differ to certain extent from those reported in previous literatures for the reactions of stable ylides in the absence of LiBr by being smaller in absolut value, nevertheless, of same sign.[2]

This situation suggests that under the present experimental conditions the mechanistic feature of the reaction might be different from that proposed by former authors for this kind of reaction though under different conditions.

The reaction rates of substituted benzaldehydes with benzylidenetriphenylphosphorane are inspected in the same way and the results are listed in Table 3.

TABLE 3. Reaction rates of substituted benzaldehydes with benzylidene-triphenylphosphorane (25°C) and substituent constants

Substituents	k . 10^2 (mole. min^{-1})	log k	σ
H	12.90	-1.89	0.00
p-CH_3	5.70	-1.24	-0.17
p-CH_3O	2.11	-1.65	-0.27
p-Cl	30.85	-0.51	0.23
m-Br	53.2	-0.27	0.39

Regression of log k against σ in the same way results in the following equation (3).

$$\log k = 1.99\sigma - 0.984 \quad (3)$$

with a correlation coefficient constant, r = 0.985, where σ is the classical substituent constants.

Reactions between Substituted Ylides and Benzaldehyde.

With a view to inspecting the effect of substituent on benzylidenetriphenylphosphorane on the reaction, various substituted phosphoranes are reacted with benzaldehyde in methanol-lithium methanolate. Rates of the reactions were measured which indicated again that electron withdrawing substituents partake of the effect of rate enhancement and electron repelling ones, on the other hand, act in reverse direction. The results are listed in Table 4.

TABLE 4. Rates of the reactions between para substituted benzylidenetriphenylphosphoranes and benzaldehyde (25°C)

Substituents	k (mole^{-1} min^{-1})	log k	σ
H	0.129	-0.887	0.00
Cl	0.812	-0.088	0.23
Br	0.927	-0.033	0.23
CH_3	0.036	-1.450	-0.17

Using least square method to correlate log k against σ gives the following equation:

$$\log k = 3.49\sigma - 0.868 \quad (4)$$

with correlation coefficient constant, r = 0.999. Plot of log k verus σ is given in Figure 2.

If σ_{im} caculated by PMMP method are employed to make the correlation, the equation thus obtained is

$$\log k = 2.67\sigma_{im} - 0.941 \quad (5)$$

with r = 0.998.

Variation of Substituents both on the Phosphoranes and the Aldehydes.[5]

Under the same conditions, the rates of the reaction between various substituted phosphoranes and various substituted aldehydes are measured. The results thus obtained are tabulated in Table 5.

TABLE 5. Values of the logarithmic rates of the reactions between substituted benzylidenetriphenylphosphoranes and substituted benzaldehydes (25°C) and the corresponding substituents and their constants

log k	X	σ_x	Y	σ_y
-1.45	p-CH_3	-0.17	H	0.00
-1.66	p-CH_3	-0.17	p-CH_3	-0.17
-0.976	p-CH_3	-0.17	p-Cl	0.23
-0.668	p-CH_3	-0.17	m-Br	0.39
-0.889	H	0.00	H	0.00
-1.24	H	0.00	p-CH_3	-0.17
-1.65	H	0.00	p-CH_3O	-0.27
-0.511	H	0.00	p-Cl	0.23
-0.274	H	0.00	m-Br	0.39
-0.088	p-Cl	0.23	H	0.00
-0.033	p-Br	0.23	H	0.00
-2.02	p-CH_3	-0.17	p-CH_3O	-0.27
-0.770	p-Cl	0.23	p-CH_3O	-0.27
-0.248	p-CH_3	-0.17	m-NO_2	0.71

*X and Y stand for the substituents on phosphorane and benzaldehyde respectively; σ_x and σ_y, the corresponding substituent constants of X and Y.

Double linear regression was made for log k versus substituent constants for X and Y, i.e., σ_x and σ_y to give

$$\log k = 3.31\sigma_x + 1.88\sigma_y - 0.926 \quad (6)$$

With double correlation coefficient constant R = 0.986.* Classical Hammett substituent constants are taken for σ_x and σ_y.

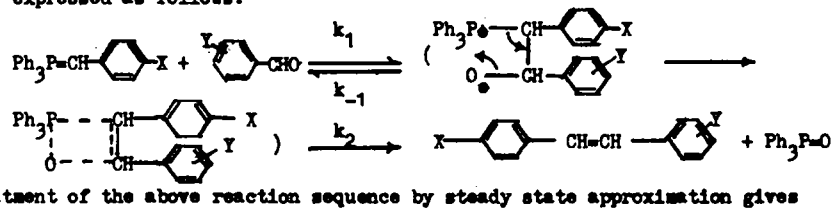
In equation (6) coefficients 3.31 and 1.88 are reaction constants, ρ_x and ρ_y which can be regarded as the sensitivity of the reaction toward the variation of substituents on phosphorane and

*Calculation was carried out on YE 8100 computer with Fortran Language.

aldehyde respectively; whereas the constant -0.926 in equation (6) is the value of log $k_{H,H}$, i.e., the corresponding logarithmic k with both X and Y being hydrogen atoms. This equation reflects the effect of substituents on both components of the reaction system on reaction rate.

On the Reaction Mechanism.

From the above experimental evidences we are in a position to give a brief accounts on the mechanism of the Wittig reaction. In previous literatures, the mechanism of this reaction is generally expressed as follows:[2]



Treatment of the above reaction sequence by steady state approximation gives

$$\frac{-d\,(Ald)}{dt} = k_1(BTP)(Ald)$$

where Ald and BTP represent aldehyde and benzylidenetriphenylphosphorane respectively, if intermediate formation is the rate determining step(rds); or

$$\frac{-d(Ald)}{dt} = K_1k_2(BTP)(Ald)$$

in case where ethylene formation is the rds, where $K_1 = k_1/k_{-1}$ is the concentration equilibrium constant.

The first supposition being the case, there should be $k_{obs} = k_1$, and

$$\log \frac{k_{obs}}{k^o_{obs}} = \log \frac{k_1}{k^o_1} = \rho_{1x}\,\sigma_x + \rho_{1y}\,\sigma_y$$

where k_{obs} is the experimentally apparent rate.

In the second case, we have $k_{obs} = K_1k_2$, then

$$\begin{aligned}\log k_{obs} &= \log K_1k_2\\ &= \log K_1 + \log k_2\\ &= \rho_{1x}\sigma_x + \rho_{1y}\sigma_y + \rho_{2x}\sigma_x + \rho_{2y}\sigma_y + C\\ &= (\rho_{1x} + \rho_{2x})\,\sigma_x + (\rho_{1y} + \rho_{2y})\,\sigma_y + C\end{aligned}$$

The experimental findings indicate that under the present reaction conditions with ylides of intermediary stability, i.e., containing aryl group on methylenic carbon, electron withdrawing substituents on both aldehydes and ylides impose rate enhancement effect on the reaction resulting in ρ_x and $\rho_y > 0$.

In case where intermediate formation is rds, the electron withdrawing groups on benzaldehyde should enhance its reactivity by increasing the electrophilicity on carbonyl carbon atom and, consequently, $\rho_{1y} > 0$. However, electron withdrawing groups on the ylide will dissipate the electron density on its methylenic carbon and thus decrease its nucleophilicity, so the electronic factor of electron withdrawing group would seem to operate against the success of the reaction and consequently we should expect an extenuatory reaction rate, i.e. $\rho_{1x} < 0$. However, the observed ρ_{obs} in equations (4) and (5) runs counter to that could be expected, should the first occurrence be the case, so the intermediate formation is unlikely the rds.

The transition state of the ethylene formation is an activated betaine from which it is more reasonable to expect that $\rho_{2y} < 0$ for benzaldehyde and $\rho_{2x} > 0$ for the ylide, in so far as the driving force of electron shift is attributed to the formation of the new phosphorus-oxygen bond in the oxaphosphetane which splits up into phosphine oxide and the olefin*. This situation suggests rather strongly that ethylene formation is the rds, since it is more pertinent to rationalise that the apparent ρ_{obs} as the sum of those of rds and the preceding step as is expected from the steady

*It is more reasonable to regard the betaine and the oxaphosphetane as the same species or, in terms of the resonance theory, the canonical forms of the hybrid.

state treatment.

The observed entropy of activation $\Delta S^{\neq}$ is likewise the sum of those of two or more steps preceding the rds of the ethylene formation.

Algebraically Additive Nature of the Hammett Equation.

Based on the above mentioned, it can be expected that electronic withdrawing substituents on components of the reaction partake of parallel effect on the reaction as shown in equation (6). The effects of the substituents attached on ylides and aldehydes separately are found as expressed in equations (3) and (4). From these equations it can be easily seen that if the ρ terms of the right hand of equations (3) and (4) are added and the average of the constant terms in both equations are taken, there will result in the following equation:

$$\log k = 3.49\,\sigma_x + 1.99\,\sigma_y - 0.926 \qquad (7)$$

Comparison of equations (6) and (7) reveals their close resemblance to each other. This implies that, in Wittig reactions under the present conditions, the effect of the substituents concurrently attached on both components can be approximately expressed as the algebraic sum of each one independent of the other. In other words, their effect on reaction rate can be approximated by taking the sum of the respective effects as if they imposed on the reaction independently to one another. To be brief, in Wittig reaction under the present conditions, the LFER partakes of an additive nature with respect to substituents on both the aldehyde and the phosphorane.

EXPERIMENTAL

Some of the substituted benzaldehydes employed in this work are commercial products which were redistilled or recrystallised according as they are liquid or solid and then stored under low temperature and nitrogen atmosphere for ready use.

Preparation of Substituted Benzyl Bromides.

In a 250 ml. round bottom flask 150 ml. (0.1 mole) of substituted toluene was reacted with about equivalent amount of NBS in the presence of small amount of benzoyl peroxide. The mixture was refluxed for 2-3 hours till NBS turned white entirely, cooled and filtered. Filtrate was concentrated and chilled to give the benzyl bromide.

Preparation of Substituted Benzyltriphenylphosphonium Bromide.[6]

To the ready prepared substituted benzyl bromide a solution of equivalent amount of triphenylphosphine in chloroform was added. After refluxing and cooling, the reaction mixture was poured into ether. The crude product was separated as white crystalline solid which was then recrystallised twice from a solvent couple composed of chloroform and ether. The purified product was then kept in a desiccator for ready use. The reaction periods of various substituted benzyl bromides with triphenylphosphine and the melting points of the phosphonium bromide are listed in Table 6.

TABLE 6. Reaction periods of substituted benzyl bromides with triphenylphosphine and the melting points of phosphonium bromides

Substituents:	H	p-CH_3	p-Cl	p-Br
reaction periods (hr./min.)	2/30	2/0	2/50	2/40
melting points(°C)	232	238	242	240

Rate Measurement.

Titration Method. 104 ml. of the solution of 0.1 M. Lithium methylate in methanol was put into a water jacketed five necked round bottom flask under nitrogen atmosphere. Water in a superthermostat and kept at an appropriate temperature (± 0.01°C) was circulated through the jacket of the reaction vessel. Equivalent amount of a phosphonium bromide was added. After elapse of 20 min. 4 ml. of the solution was taken from the flask and titrated with standardised 0.05 N. HCl-C_2H_5OH to obtain the initial concentration C_o. Equimolar substituted benzaldehyde was added. 4 ml. aliquots of the reaction solution were taken at intervals and poured into 20 ml. absolute ethanol at 0-5°C. Bromophenol blue being employed as indicator, the solution was titrated with standard 0.05N. HCl-C_2H_5OH till it turned yellow. The residual concentration of the ylide $C = N_{HCl} \cdot V_{HCl}/4$. Using least squal method to make the linear regression of 1/C versus t, the correlation coefficient and regressive equation $1/C = a + bt$ were found out with b corresponding to the rate constant.

High performance liquid chromatographic method. Chromatography was carried out on Shimadzu LC-4A HPLC; column:SIL 10 m, 4.6×250mm; mobile phase, chloroform:hexane:IPA = 35:60:5; flow rate 1 ml/min.; pressure 34 kg/cm². Five portions of solution of the corresponding benzaldehyde in hexane of different concentrations were prepared and their peak heights were measured. Reference equation for the relationship between the peak height and the concentration was derived. Reaction was run under the conditions referred to above and aliquots of reaction mixtures were taken at intervals and after dilution with n-hexane, were injected into the chromatography. The concentrations of aldehydes in the reaction system was obtained from the peak height in conjunction with the reference equation.

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