

# Kinetic studies on the reaction between substituted benzyl phosphonates and substituted benzaldehydes

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**(received 08 Oct 04; accepted 08 Jan 05; published on the web 18 Jan 05)**

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## Abstract

The kinetics of Wittig-Horner reaction between several middle-active phosphonates and substituted benzaldehydes, and the effect of substituents which bond on phosphonates and benzaldehydes respectively on the reaction rate have been studied. Experimental findings are consistent with intermediate formation being the rate-determining step. The substituents on phosphonates play an important part in the formation of the intermediate. Large negative entropy values provide further evidence for the rate-determining step, and for the intermediate, which probably has a four-membered cyclic structure.

**Keywords:** Wittig-Horner reaction, phosphonates, substituted benzaldehydes, kinetic studies, intermediate

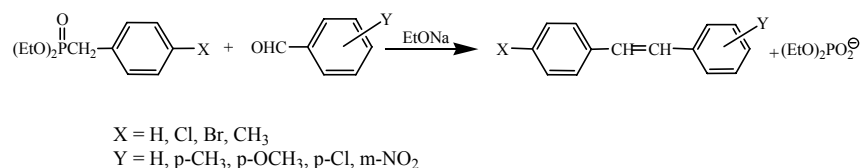
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## Introduction

Since 1958, when Horner and coworkers<sup>1</sup> first described that phosphonate carbanions can replace Wittig reagent to react with carbonyl compounds. The reaction as a synthetic method has been studied widely. Due to the higher nucleophilicity of phosphonate carbanions, the reaction occurs under milder conditions than the conventional Wittig-reaction, and the products can be easily isolated from the reaction mixture.<sup>2</sup>

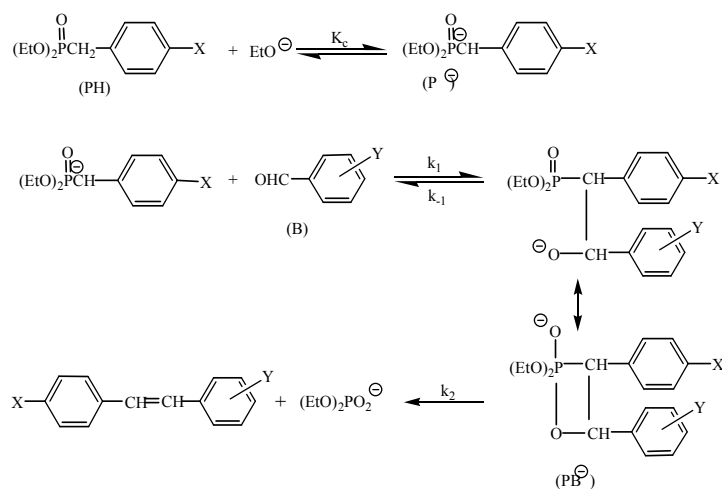
The mechanism of Wittig-Horner reaction has been well studied.<sup>3-5</sup> But a great part of these was based on the stereochemistry of olefin formation until the reaction kinetics for the reaction of phosphoryl-stabilized carbanions and substituted benzaldehydes was studied by Larson and Aksnes. They proposed a reaction mechanism from these kinetic studies which involves a four-membered cyclic structure as the reactive intermediate. In this paper, we have studied the kinetics of Wittig-Horner reaction between several moderately active phosphonates and substituted benzaldehydes, by observing the effect of varying substituents on the phosphonates

and benzaldehydes respectively and calculating the activation parameters of this reaction. From above-mentioned results, we propose the reaction mechanism.



## Results and Discussion

Larsen and Zhao's results indicate that the reaction are overall third order. First order in phosphonate, ethoxide, and aldehyde respectively.<sup>6-8</sup> The mechanism of the reaction may be expressed as follows.



In accordance with steady state approximations, the following rate equation can be given:

$$\text{rate} = \frac{k_1 k_2 K_c}{k_2 + k_{-1}} [\text{PH}] [\text{EtO}^-] [\text{B}].$$

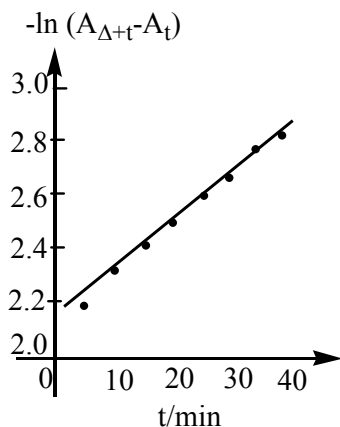
Where [PH], [B] and [EtO<sup>-</sup>] represent the concentration of phosphonate, aldehyde and base respectively. Under pseudo first order reaction condition, [PH], [EtO<sup>-</sup>]<sup>>></sup>[B]. Consequently, [PH] [EtO<sup>-</sup>] would be seen as a constant, we can obtain following equation:

$$\text{rate} = k [\text{PH}][\text{EtO}^-][\text{B}] = k_{\text{obs}}[\text{B}], \quad k_{\text{obs}} = k[\text{PH}][\text{EtO}^-]$$

The progress of reaction was followed by measuring the absorbance(A) of the substituted aromatic aldehydes or product alkenes, and the equation below was established

$$\ln (A_{\Delta+t}-A_t) = \ln (A_{\infty}-A_0)-k_{\text{obs}} \cdot t + \ln (1-e^{-k_{\text{obs}} \cdot \Delta})$$

The pseudo first order observable rate constants were obtained from the slope of the straight line of the plot of  $\ln (A_{\Delta+t}-A_t)$  versus time t (**Figure 1**) and then k was calculated from it.



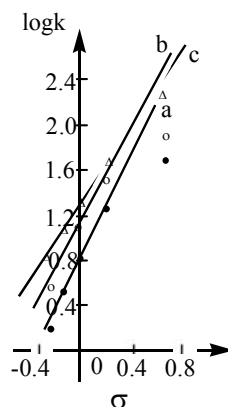
**Figure 1.** Reaction straight line between diethyl benzyl phosphonate and benzaldehyde at 27 °C.

A series of rate constants and corresponding correlation coefficients between diethyl benzyl phosphonate and various substituted benzaldehyde were obtained at different temperatures and the results are listed in **Table 1**.

**Table 1.** Rate constants (k) and corresponding correlation coefficients ( $\gamma$ ) of the reaction between diethyl benzyl phosphonate and various substituted benzaldehydes

Temperature(°C)	k( $\gamma$ ) for various substituted benzaldehydes				
	H	<i>p</i> -CH <sub>3</sub>	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -Cl	<i>m</i> -NO <sub>2</sub>
27.0	6.577	3.613	1.638	19.30	58.21
	(0.997)	(0.951)	(0.957)	(0.974)	(0.994)
35.4	12.04	6.727	4.287	37.20	113.1
	(0.998)	(0.987)	(0.985)	(0.992)	(0.993)
45.4	21.15	11.25	7.001	47.12	176.5
	(0.991)	(0.999)	(0.997)	(0.987)	(0.982)

Correlation of log k with a series of the corresponding Hammett  $\sigma$  values gives satisfactory linear relationship (**Figure 2**). Using the least squares method gives the following equations and corresponding correlation coefficient constants **Table 3**.



**Figure 2.** Effect of the substituents on aldehydes and phosphonates on rate.

**Table 2.** Regressive equation of the reaction between diethyl benzyl phosphonate and aldehydes at different temperature

Temperature (°C)	Regressive equation	P	$\gamma$
27.0	$\log k = 2.05\sigma + 1.15$	2.05	0.992
35.4	$\log k = 1.85\sigma + 1.42$	1.85	0.988
45.4	$\log k = 1.64\sigma + 1.57$	1.64	0.996

As shown in **Table 2**, the substituents on the benzaldehyde can influence the reaction rate greatly. The positive sign of the reaction constant,  $\rho$ , indicates that the reaction is accelerated by electron withdrawing substituent groups in the *p*- and *m*-positions in the aromatic aldehydes and by increasing the reaction temperature.

The calculated reaction constant,  $\rho$ , in the Wittig-Horner reaction is considerably lower than that of the analogous Wittig-reaction of ester-stabilized ylides, where  $\rho$  is in the range 2.7~3.0. The difference is attributed to the much greater nucleophilicity of the phosphoryl stabilized carbanions when compared to the corresponding ylides.

The result that electron-withdrawing groups enhance, and electron-donating groups decrease the reaction rate is obtained in the same way with the reaction between various substituted diethyl benzyl phosphonates and benzaldehyde. The resulting constants are listed in **Table 3**.

**Table 3.** Rate constants (*k*) and corresponding correlation coefficients ( $\gamma$ ) of the reaction between substituted benzyl diethyl phosphonates and benzaldehyde at 27 °C

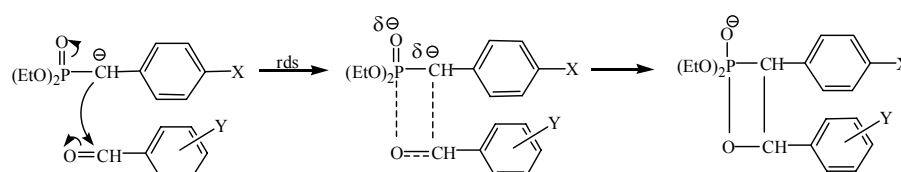
Substituents	H	<i>p</i> -CH <sub>3</sub>	<i>p</i> -Cl	<i>p</i> -Br
<i>k</i> ( $\gamma$ )	6.577 (0.997)	1.829 (0.973)	41.84 (0.993)	43.09 (0.993)

Regression of  $\log k$  against the general substituent constants  $\sigma$  gave the following equation with a correlation coefficient constant,  $\gamma = 0.999$ .

$$\log k = 3.43\sigma + 0.84$$

$\rho$  Values of the reaction between diethyl benzylphosphonate and substituted benzaldehydes were compared with those of the reaction between substituted diethyl benzylphosphonates and benzaldehyde, we found that all of them are positive and the former is greater; which indicates that substituents on the phosphonates have a great effect on the reaction rate.

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. The structure of the reaction intermediate is described as follows.



Experimental findings obtained are consistent with intermediate formation in the rate-determining step, since electron withdrawing groups on phosphonate decrease its basicity, enhance its nucleophilicity and benefit the intermediate formation. Consequently, the reaction rate is increased. So the substituents on phosphonates play an important part in the formation of intermediate. However, electron withdrawing groups on benzaldehyde only increase its electrophilicity and don't benefit the intermediate formation, this result was identified by us with competitive reactions of benzaldehyde and *p*-nitrobenzaldehyde for the dibutyl  $\alpha$ -naphthylmethylphosphonate, so X groups have a greater effect on rate than Y groups. This is why the former  $\rho$  value is greater than the latter.

Finally, as shown in **Table 4**, the activation parameters  $\Delta E^\ddagger$  and  $\Delta S^\ddagger$  were calculated according to the correlations between  $\ln k$  obtained above and the corresponding inverse temperature ( $1/T$ ) when the rate constants  $k$  were experimentally measured at 27 °C, 35.4 °C and 45.4 °C.

**Table 4.** Activation parameters of the reaction between diethyl benzylphosphonate and substituted benzaldehydes

Substituents	H	<i>p</i> -CH <sub>3</sub>	<i>p</i> -OCH <sub>3</sub>	<i>p</i> -Cl	<i>m</i> -NO <sub>2</sub>
$\Delta E^\ddagger$ (KJ.mol <sup>-1</sup> )	51.16	52.35	65.82	44.34	52.91
$\Delta S^\ddagger$ (J.K <sup>-1</sup> )	81.96	82.94	43.04	94.68	57.67
$\gamma(\ln k - 1/T)$	0.984	0.982	0.963	0.959	0.975

Large negative entropy values in **Table 4** provide further evidence to support that the rate-determining step is intermediate formation and the intermediate likely has a four-membered cyclic structure.

## Experimental Section

**General Procedures.** All substituted benzaldehydes were purchased and redistilled or recrystallized according as they are liquid or solid and then stored under nitrogen atmosphere for ready use. Various substituted benzyl bromide were prepared by Zhao's method from the substituted toluene.<sup>8</sup> MS spectra data were recorded on Finnigan MAT-4510 mass spectrometer. <sup>1</sup>H NMR spectra were measured on a Varian INOVA-400 spectrometer and chemical shifts in ppm are reported relative to internal Me<sub>4</sub>Si (CDCl<sub>3</sub>). Elemental analyses were performed by using a Carlo-Elba 1106 elemental analytical instrument. Melting points were determined by using a micro-melting point apparatus without any corrections.

**Preparations of substituted diethyl benzyl phosphonates.** Under nitrogen atmosphere, benzyl bromide (17 g, 0.1 mol) was heated and stirred with excess triethyl phosphite (33.2 g, 0.2 mol) to 150-160 °C for 3 h, and then distilled under reduced pressure. The product is collected at 166-168 °C/4mm. The yield of colorless product is 14.7 g (64.6%),  $n_D^{21}=1.4892$ .  $\nu$  (cm<sup>-1</sup>): 3063 (Ar-H), 1250 (P=O); <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 7.28 (s, 5H, ArH), 5.70 (s, 2H, CH<sub>2</sub>), 3.84-4.16 (m, 4H, CH<sub>2</sub>), 1.15-1.31 (t, 6H, CH<sub>3</sub>); MS-EI (m/z): 228 (M<sup>+</sup>); HRMS: 228.2248 (Calcd. 228.2246).

***p*-Methylbenzyl diethyl phosphonate** in 47.3% yield, b.p. 164-165 °C (4 mm),  $n_D^{21}=1.4940$ .  $\nu$  (cm<sup>-1</sup>): 3065 (Ar-H), 1252 (P=O); <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 7.16-7.24 (m, 4H, ArH), 5.72 (s, 2H, CH<sub>2</sub>), 3.80-4.12 (m, 4H, CH<sub>2</sub>), 2.37 (s, 3H, CH<sub>3</sub>), 1.12-1.28 (t, 6H, CH<sub>3</sub>); MS-EI (m/z): 242 (M<sup>+</sup>); HRMS: 242.2530 (Calcd. 242.2512).

***p*-Chlorobenzyl diethyl phosphonate.** 40% yield, b.p. 178-180 °C (5 mm),  $n_D^{27.5}=1.5020$ .  $\nu$  (cm<sup>-1</sup>): 3068 (Ar-H), 1250 (P=O); <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 7.45-7.50 (d, 2H, ArH), 7.26-7.30 (d, 2H, ArH), 5.78 (s, 2H, CH<sub>2</sub>), 3.78-4.12 (m, 4H, CH<sub>2</sub>), 1.17-1.34 (t, 6H, CH<sub>3</sub>); MS-EI (m/z): 263 (M<sup>+</sup>); HRMS: 262.6673 (Calcd. 262.6697).

***p*-Bromobenzyl diethyl phosphonate.** 46.5% yield, b.p. 192.5-195 °C (5 mm),  $n_D^{26}=1.5179$ .  $\nu$  (cm<sup>-1</sup>): 3065 (Ar-H), 1252 (P=O); <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 7.60-7.76 (d, 2H, ArH), 7.10-7.24 (d, 2H, ArH), 3.86-4.18 (m, 4H, CH<sub>2</sub>), 1.18-1.36 (t, 6H, CH<sub>3</sub>); MS-EI (m/z): 307 (M<sup>+</sup>); HRMS: 307.1242 (Calcd. 307.1207).

Sodium ethoxide in ethanol was prepared by dissolving fresh-cut sodium-metal in anhydrous ethanol under nitrogen atmosphere. Sodium ethoxide solution was obtained by adding DMF to make that the volume of ethanol was equal to that of DMF, and the concentration was standardized by standardized hydrochloric acid.

**Kinetic measurements.** The reaction rates of phosphonates with various substituted benzaldehydes were measured by monitoring the ultraviolet absorption spectra of olefins or aldehydes. The reactions were performed under pseudo first order condition with phosphates and NaOEt in large constant excess. The pseudo first order rate constants were obtained from the slope of a plot of  $\ln[A_{\Delta+t}-A_t]$  against time  $t$ , where  $A_t$  is the absorbance at time  $t$  and  $\Delta$  is a constant time interval.

The reaction was started by adding a small volume of aldehyde solution ( $\sim 10 \mu\text{L}$ ) to a septum-capped UV-cell containing the freshly prepared solution of the sodium ethoxide and phosphonates. The reaction was continued about 90 min, and a data can be taken down per 5 min.

## Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (20132020, 20372051), the Teaching and Research Award Program for Outstanding Young Teachers in Higher Education Institutions of MOE, Specialized Research Fund for the Doctoral Program of Higher Education and Scientific Fund of Sichuan Province for Outstanding Young Scientist.

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