

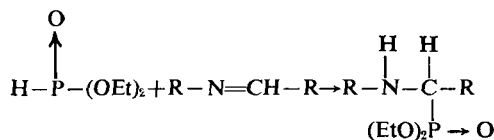
Kinetic Study of the Nucleophilic Addition of Diethyl Phosphonate to Benzyldeneanilines

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Abstract □ The kinetics of the base-catalyzed addition of diethyl phosphonate to some substituted benzyldeneanilines were measured by observing the disappearance of the Schiff bases spectrophotometrically. A first-order dependence of the rate on diethyl phosphonate, Schiff base, and ethoxide ion concentration was observed. An atypical Hammett relationship was obtained and a hypothesis advanced which explained the bending of the Hammett plot. The reaction mechanism proposed is discussed in relationship to the spectra and other experimental data.

Keyphrases □ Schiff bases—synthesis □ Benzyldeneanilines—diethyl phosphonate addition □ Kinetics—base-catalyzed benzyldeneaniline reaction □ UV spectrophotometry—reaction monitoring

Phosphorus compounds are involved in human metabolism almost ubiquitously, yet very few studies have been undertaken to examine the fundamental chemistry of organophosphorus compounds, particularly reactions involving phosphorus-carbon bond formation. Fields (1), in 1952, published several syntheses of substituted dialkyl alkylaminomethyl phosphonates. One of the methods utilized by Fields was the reaction between dialkyl phosphonates and Schiff bases shown in Scheme I.



Scheme 1

Other reactions of phosphorus compounds with double bonds are known; for example, free radical reactions between olefins and various phosphorus compounds have been reviewed in detail (2). However, the reaction reported by Fields is particularly suitable for kinetic studies because of the high yields and the applicability of spectrophotometric means of analysis.

This laboratory (3) previously measured the rate of reaction of diethyl phosphonate with a series of Schiff bases carrying substituents on the phenyl group attached to the carbon atom of the carbon-nitrogen double bond. A proposed mechanism involving the nucleophilic addition of the diethyl phosphonate anion to the Schiff base was consistent with observed kinetic data and Hammett plot. The purpose of the present study is to extend the previous study to compounds carrying the substituent on the phenyl group attached to the nitrogen of the carbon-nitrogen double bond in an effort to provide more detailed information concerning the nature of the process of carbon-phosphorus bond formation.

Table I—Properties for the Schiff Bases

Schiff Base Substituent	Exp. m.p., °C. ^a	Rep. m.p., °C.	Ref.
—H	51–52	52	4
—Br	65–66	66	4
—CO ₂ CH ₃ ^b	107–108	—	—
—OCH ₃	70.5–71.5	70–71	4
—N(CH ₃) ₂	97.5–98.5	97.5–98.5	16

^a Melting points are uncorrected. ^b Anal.—Calcd. for $C_{15}H_{11}NO_2$: C, 75.35%; H, 5.43%; N, 5.86%. Found: C, 75.20%; H, 5.57%; N, 6.02%.

EXPERIMENTAL

Synthesis of the Schiff Bases—The Schiff bases were synthesized from benzaldehyde and the appropriate *para*-substituted anilines (4) by mixing 0.2 mole of each reactant in 20 ml. of absolute ethanol and heating on a steam bath for 15 min. In all cases, the Schiff bases crystallized upon cooling overnight. The bases were recrystallized from methylcyclohexane a minimum of two times, or until the melting point remained constant. The properties of the Schiff bases are given in Table I.

Determination of Schiff Base Molar Absorptivity—Three solutions of varying concentrations of each Schiff base were made using anhydrous ethanol in clean, previously dried, modified volumetric flasks.¹ Four dilutions of each original concentration of Schiff base solution were made and the spectra scanned on a Beckman DB spectrophotometer.² The absorbance was read in 1-cm. quartz cells at five chosen wavelengths over 10-m μ intervals by using the DB programmer attachment in the preselect mode. The particular five wavelengths (Table II) utilized for each Schiff base were chosen on the basis of the shape of each spectral curve. The portion of the spectral curve utilized in each case was outside the area of the spectrum of the diethyl phosphonate or the addition product produced. The concentrations used and the absorbances observed were tabulated for each wavelength and punched on IBM data cards. The data were processed on a computer³ and the molar absorptivity with standard deviations calculated by a least-squares average program.

Preparation of Solvent and Reactants—Seven grams of sodium was dissolved in 1 l. of commercial absolute ethanol.⁴ After solution of the sodium was complete, 30 ml. of diethyl *o*-phthalate⁵ was added to the solution and refluxed for 2 hr. (5, 6). The first and last 10% of the distillate was discarded and the middle 80% of the distillate collected for use. The receiving flask, previously dried in a 120° oven, was cooled by air which had been passed through a phosphorus pentoxide drying tube, flamed, and cooled again before being used to collect the distilled ethanol.

Commercial diethyl phosphonate⁶ was vacuum-distilled twice after being received, then stored in a new container in a refrigerator. The previously distilled diethyl phosphonate was vacuum-distilled daily for reaction use. The appropriate volume of daily vacuum-distilled diethyl phosphonate was pipetted into a volumetric flask partially filled with anhydrous ethanol, mixed thoroughly, brought

¹ See *Rate Constant Determination Procedure*.

² Model DB, Beckman Instruments, Inc., Fullerton, Calif.

³ North Dakota, State University IBM 1620 computer.

⁴ U.S. Industrial Chemicals, Tuscola, Ill.

⁵ Fisher Scientific Co., Chicago, Ill.

⁶ K & K Laboratories, Inc., Plainview, N.Y.

Table II—Molar Absorptivity of the Schiff Bases in Absolute Ethanol at the Wavelengths Employed for the Determination of the Rate Constants

Wavelength, $m\mu$	Benzylidene-aniline	Benzylidene- <i>p</i> -bromo-aniline	Benzylidene- <i>p</i> -carbo-methoxy-aniline	Benzylidene- <i>p</i> -methoxy-aniline	Benzylidene- <i>p</i> -dimethyl-amino-aniline
440					1591
430					3061
420					5426
410					8637
400					1, 1719
370	486	739	1129	360	
360	1156	1909	2437	651	
350	2449	4144	4696	988	
340	4376	6675	7507	1202	
330	6147	9030	10066	1249	

to volume, and capped. This solution was then used to make the reaction solutions.

The catalyst solution was prepared by dissolving an appropriate amount of sodium in a volumetric flask which had been previously dried in a 120° oven, cooled, and partially filled with the anhydrous ethanol. The flask was weighed immediately after introduction of the sodium which had been rinsed in anhydrous ethanol to remove all traces of oxide and mineral oil under which it was kept. After solution of the sodium was complete and the flask cooled to room temperature, it was brought to volume with the anhydrous ethanol and capped.

The Schiff bases were weighed out in previously dried 50-ml. volumetric flasks and then partially filled with anhydrous ethanol to effect solution. After solution was complete, the solutions were brought to volume and capped.

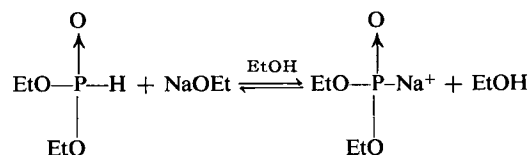
Rate Constant Determination Procedure—The reaction flasks with large diameter neck tops were made by fusing a section of larger diameter glass tubing to the shortened original neck of the flask. The large tops made possible the use of fold-over rubber septums for sealing the flasks after the reaction solution components were added. These flasks were washed with isopropanol only and kept in a 120° oven when not actually in use. The rubber septums were soaked in acetone for 3 hr., rinsed, and soaked again for 3 hr., rinsed, and air-dried (7). The septums were then placed in a vacuum desiccator and evacuated for several hours. The septums were kept in a vacuum desiccator until used.

An appropriate aliquot of the Schiff base solution was pipeted into one of the capped, cooled reaction flasks just previously partially filled with anhydrous ethanol. The proper amount of diethyl phosphonate was pipeted into the reaction flask. As the sodium ethoxide aliquot was pipeted into the reaction flask, the time was noted on the recorder. The solution was immediately brought to volume with a hypodermic syringe and capped with a fold-over rubber septum. After shaking, the flask was placed in the water bath. The flasks were kept tightly closed at all times except when actual pipeting of the reactant solutions took place. It was determined early in the course of the study that a temperature and kinetic rate equilibration time of about 40 min. was needed before initiating sampling. Rate deviations occurred when the reaction was carried far in excess of 90% of completion. The runs were, therefore, stopped at approximately 90% of the completion. This was achieved by calculating the theoretical absorbance at the wavelength employed when the reaction was 90% complete.

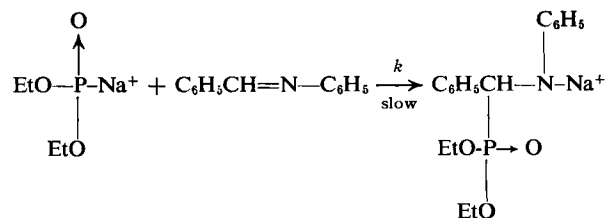
The sampling was done by withdrawing 3-ml. samples from the reaction flasks with a 10-ml. hypodermic syringe. The sample was placed in a 1-cm. quartz cell, the time noted on the recording paper, and the absorbance read at the chosen five wavelengths using the spectrophotometer in preselect mode. The syringe and cell were rinsed in anhydrous methanol and air-dried between samples. A minimum of six samples was taken from each run except when the rate of the reaction was high. The experimental data included: the number of wavelengths used, the wavelength interval in $m\mu$, the absorptivity at the respective wavelengths, date and run number, initial and final concentrations, total number of samples taken, cycle number (minutes since reaction started), time conversion factor, and observed absorbance at the respective wavelengths for each sampling. The spectrophotometric data enumerated was then read into a computer.

The calculation of the concentrations of the Schiff base was carried out by a least-squares technique. Included in this calculation was a component which has a constant absorbance (error component) at all wavelengths used. The concentration of this error component is computed simultaneously with the concentration of the Schiff base by the least-squares technique. The error component allows the calculation of the Schiff-base concentration to be made with optimum accuracy by elimination of linear error. The program completes the calculation of the Schiff-base concentration at each time interval, calculates the pseudo first-order rate constant at each of the time intervals. Next, a least-squares calculation of the pseudo first-order rate constant is carried out, then the program selects an optimum value by an iterative method for the infinity concentration of the Schiff base, recalculates the rate constants, and punches the output on cards so that a complete summary of the various values can be rapidly printed. The least-square pseudo first-order rate constant was the value utilized for calculating the third-order rate constant. These are summarized in Table III.

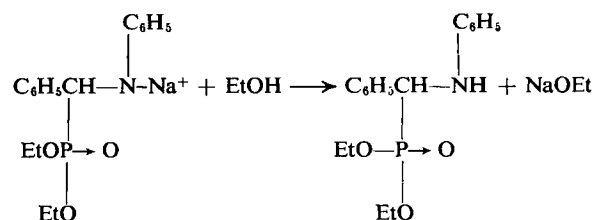
Discussion—The mechanistic sequence proposed is basically the same as that of Hopkins (3) who studied the effect of *para*-substitution on the C-phenyl ring of benzylideneanilines in nucleophilic addition of diethyl phosphonate. In both Hopkins' and this work, overall third-order kinetics were observed. If the differential equations are set up for the reaction sequences shown below, one obtains an equation consistent with the observed kinetics. The proposed mechanistic sequence is seen in Schemes II–IV.



Scheme II



Scheme III



Scheme IV

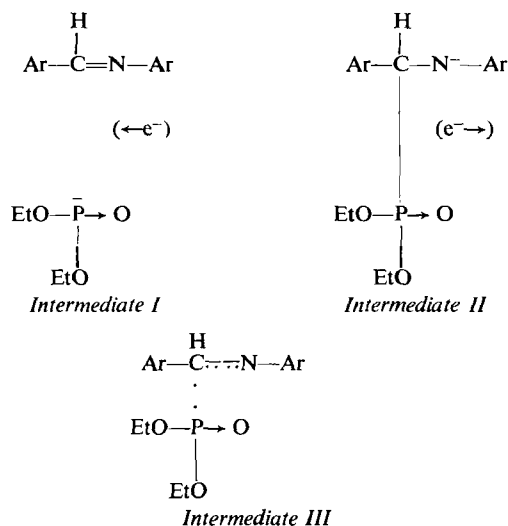
Table III—Kinetic Data Summary^a

Benzyl- ideneaniline Substituent	Tempera- ture, °C.	Third-Order Rate Constant, l. ² /m. ² /sec. ⁻¹
<i>p</i> -CO ₂ CH ₃	30	6.559 ± 0.834 × 10 ⁻¹
<i>p</i> -H	30	2.933 ± 0.178 × 10 ⁻² (3)
<i>p</i> -OCH ₃	30	7.583 ± 0.207 × 10 ⁻³
<i>p</i> -CO ₂ CH ₃	40	1.260 ± 0.0276
<i>p</i> -Br	40	3.662 ± 0.0484 × 10 ⁻¹
<i>p</i> -H	40	5.320 ± 0.0156 × 10 ⁻²
<i>p</i> -OCH ₃	40	1.418 ± 0.206 × 10 ⁻²
<i>p</i> -N(CH ₃) ₂	40	7.484 ± 0.273 × 10 ⁻³
<i>p</i> -CO ₂ CH ₃	50	2.029 ± 0.153
<i>p</i> -H	50	9.666 ± 0.109 × 10 ⁻² (3)
<i>p</i> -OCH ₃	50	3.057 ± 0.016 × 10 ⁻²

^a From eight to 30 runs were made per compound at each temperature with continuous concentration variation of each reactant and catalyst.

The additional information obtained in this study permits a more precise definition of the transition state of the reaction.

The resonance structures of the reaction intermediates are shown below.



Intermediate I represents a theoretical extreme under the influence of strong electron-donating substituents in the *para* position of the aniline ring while Intermediate II represents a theoretical extreme under the influence of strong electron-withdrawing substituents. The actual transition state is represented by Intermediate III with characteristics tending towards I or II depending on the specific substituent present in the molecule.

Nonlinear Hammett plots have been reported in the case of aromatic aldehyde-ammonia or amine additions (8, 9) and other reactions such as semicarbazone formation (10) and imidazole-catalyzed hydrolysis of esters (11). There are two general types of nonlinear Hammett plots usually observed: a sharply breaking bilinear plot (see Fig. 1) or a continuously curving plot. The bilinear type is more common and suggests a change in mechanism at a given point, while the curving plot is indicative of a continuous change in mechanism (12). A nonlinear Hammett plot indicates some change in the mechanistic behavior of the system under study. The change may be gross mechanistic revision, a change in the rate-determining step, or a more subtle change in the electronic characteristics of the transition state as is believed to be the case in this study. A bend in an otherwise linear Hammett plot could be indicative of a two-step reaction such as the addition of a proton to the negatively charged nitrogen of the Schiff base in Scheme IV of the proposed mechanism. This possibility is unlikely because protonic addition is usually very rapid and would not likely become a rate-determining step. A nonlinear (bent) Hammett plot of a single-step reaction would most likely imply a change in mechanistic interaction, probably electronic in nature. This would be consistent with the proposed mechanism.

The observed Hammett rho values are positive, but exhibit marked numerical difference from the negative to the positive sigma

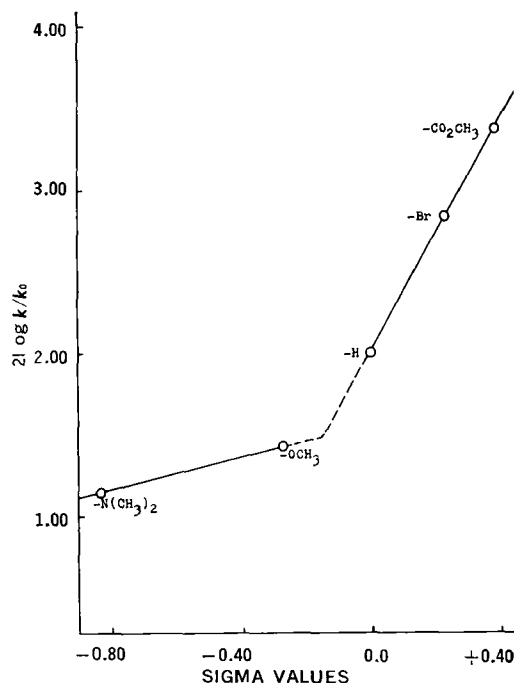


Figure 1—Hammett plot (40°) for the *para* N-phenyl-substituted Schiff bases used.

Table IV—Reaction Parameters for Hammett Plot^a

—Negative Sigma Values— Temp., °C.	rho	—Positive Sigma Values— Temp., °C.	rho
30	0.496	30	3.57
40	0.495	40	3.61
50	0.498	50	3.51

^a See Fig. 2.

side of the plot (see Fig. 1, Table IV). The rho value for the positive sigma substituents indicates that electron withdrawal markedly increases the rate of reaction. The negative sigma substituents exhibit a smaller positive rho value indicating that electron-donating substituents have a comparatively small effect on the rate of reaction although reaction is still favored by a low-electron density at the reaction site. If the carbon-phosphorus bond in the transition state (Intermediate II) is well-developed as proposed in the case of electron-withdrawing substituents, a highly positive rho value would be anticipated. This is due to the electron-withdrawing substituents assisting delocalization of the developing negative charge on the nitrogen of the carbon-nitrogen double bond. At the opposite extreme where the carbon-phosphorus bond is undeveloped (Intermediate I), the rho value would be expected to be positive but of lower magnitude than the previous case. With electron-donating substituents present, the developing negative charge on the nitrogen of carbon-nitrogen double bond is less capable of being delocalized. This charge localization will reduce the rate of attack by the incoming phosphonate anion. The change in electronic structure of the intermediates could result in the observed nonlinear Hammett plot.

Delocalized charge in the transition state would result in less solvation, and a lower negative entropy and, conversely, charge localization results in greater solvation and higher negative entropy. These expectations were confirmed by the activation parameters (Table V).

Table V—Activation Parameters

Schiff Base Substituent	Mean Entropy, e.s.u.	Energy of Activa- tion kcal./mole
—OCH ₃	—19.74	13.56
—H	—17.31	11.16
—CO ₂ CH ₃	—11.05	8.18

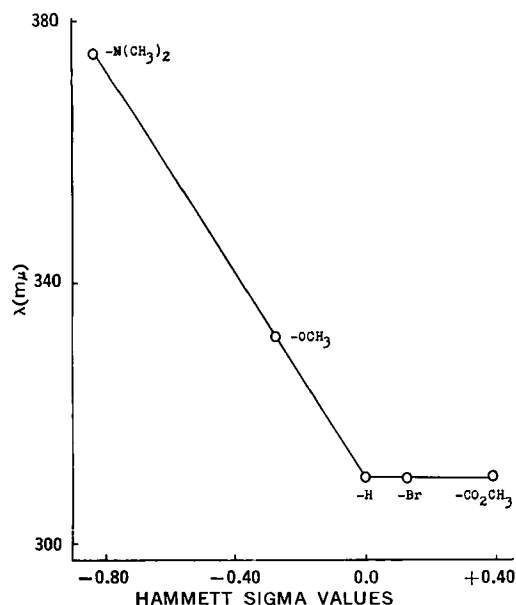


Figure 2—Spectral shift-Sigma value correlation for the para *N*-phenyl-substituted Schiff bases used.

The bathochromic shift of the lambda-max. of the peak caused by whole molecule resonance (Fig. 2) indicates the positive sigma substituents do not affect molecular conformation. In contrast to this, there appears to be a linear relationship between the negative sigma constants and the shift in lambda-max. This could be ascribed to the twisting of the *N*-phenyl ring of the benzylideneaniline molecule closer to molecular planarity when electron-donating substituents are present. A similar spectral relationship was observed by Oki and Kiyoshi (13) in a series of *N*-benzylanilines. The relative bathochromic shift of the lambda-max. was proportionate to the sigma value of electron-donating substituents in the *para* position of the *N*-phenyl ring. Brocklehurst (14) studied the UV spectra of stilbene and benzylideneanilines to ascertain why a great dissimilarity of UV spectra existed when the compounds were quite similar structurally. By four different approaches to the problem, Brocklehurst found that when the molecules under study were limited to a planar conformation, their UV spectra resembled *trans*-stilbene quite closely. Molecules with free rotation exhibited a decrease in their absorptivity. This behavior was attributed to conjugation of the unshared electron pair of the nitrogen with the *N*-phenyl ring. Smith (15), in a subsequent theoretical study, confirmed Brocklehurst's work by applying linear combination of atomic orbitals-molecular orbitals (LCAO-MO) theory and calculations to the absorption spectra of Schiff bases.

The conformational twisting toward coplanarity is a possible explanation for the reduced positive rho value exhibited by the com-

pounds with electron-donating substituents. Although the electronic changes in the transition state might not singlehandedly result in bending the Hammett plot, the additional factor of the *N*-phenyl ring twisting could cause a bend in the Hammett plot.

The reaction scheme and mechanism proposed is consistent with the experimental data and satisfactorily explains the nonlinear Hammett plot, the rho values observed, and the computed activation parameters.

SUMMARY

1. Third-order kinetics have been observed for the nucleophilic addition of diethyl phosphonate to several benzylideneanilines employing sodium ethoxide as the catalyst and anhydrous ethanol as the solvent.
2. A nonlinear Hammett relationship was observed.
3. The appropriate activation parameters were computed.
4. A mechanism which is consistent with the experimental data and computed parameters has been proposed.

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