Kinetics of the Addition of Diethyl Phosphonate to Various *p*-Substituted Benzylideneanilines

LOLA V. HOPKINS, JAMES P. VACIK, and WILLIAM H. SHELVER▲

Abstract □ The kinetics of the base-catalyzed addition of diethyl phosphonate to some substituted benzylideneanilines were measured by observing the disappearance of the Schiff bases spectrophotometrically. A first-order dependence of the rate of diethyl phosphonate, Schiff base, and ethoxide-ion concentration was observed. A typical Hammett relationship was obtained. The reaction mechanism proposed is discussed in relationship to the kinetics, the Hammett plot, and activation parameters.

Keyphrases □ Benzylideneanilines, *p*-substituted—diethyl phosphonate addition kinetics □ Diethyl phosphonate—reaction with *p*-substituted benzylidene portion of Schiff bases, mechanism of action □ Schiff bases—rate of disappearance used to study kinetics of diethyl phosphonate addition to *p*-substituted benzylideneanilines

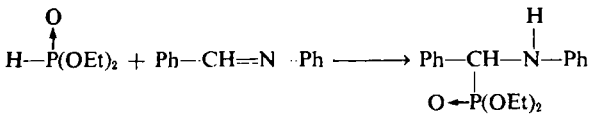
Little theoretical work has been reported on the mechanism of carbon–phosphorus bond formation, although compounds containing carbon–phosphorus bonds have been found in natural products possessing biological activity (1). Fields (2), in 1952, reported a reaction which seemed especially suitable for kinetic study by virtue of its high yield. This reaction (Scheme I) involved the addition of diethyl phosphonate to the carbon–nitrogen double bond of Schiff bases. Since the conjugated chromophore of the Schiff base is destroyed in the reaction, disappearance of the Schiff base should be easily observed spectrophotometrically. The purpose of this investigation was to elucidate the mechanism of the reaction of diethyl phosphonate with Schiff bases substituted in the *para*-position of the benzylidene portion of the Schiff bases.

DISCUSSION

The spectra of the various benzylideneanilines were measured at 10-nm. intervals, and the molar absorptivities were calculated by the normal least-squares procedure. The analytical wavelength was selected so the absorbance was minimal at the completion of the reaction. The wavelengths selected for analysis and the absorptivity are recorded in Table I.

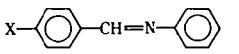
At the beginning of the study, very erratic results were noted, indicative of impure starting materials. With increased purity of the diethyl phosphonate, it was observed that the uncatalyzed reaction proceeded slowly and produced erratic results. Further investigation of the base-catalyzed reaction revealed that even trace quantities of water in the alcohol slowed the reaction tremendously. With daily preparation of the anhydrous alcohol and daily distillation of diethyl phosphonate, reproducible results were obtained (Table II).

The reaction was first order in Schiff base, diethyl phosphonate, and sodium ethoxide, and these results are compatible with the mechanism shown in Scheme II.



Scheme I

Table I—Analytical Wavelengths of Molar Absorptivities in Absolute Ethanol for the Benzylideneanilines[a]



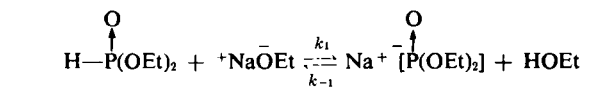
Substituent X	Analytical Wavelength, nm.	Molar Absorptivity[b]
NMe_2	355	33,910
H	350	2,385
Cl	360	1,674

[a] All spectra were determined on a Beckman model DU spectrophotometer using 1.00-cm. cells. [b] Determined by a normal least-squares procedure.

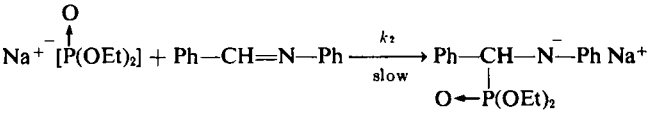
Step I is an equilibrium between diethyl phosphonate, a weak acid, and sodium ethoxide. Proton-exchange reactions of this type generally occur rapidly and are not expected to be rate determining. Step II involves formation of a carbon–phosphorus bond and would be expected to be rate determining. Since Step III is a proton exchange regenerating the base, this step is not expected to be rate determining. Utilizing the above assumptions, one may derive the following expression for the reaction rate:

$$-d(SB)/dt = \frac{k_2 \cdot k_1}{k_{-1}} \cdot \frac{(\text{Schiff base})(\text{phosphonate})(\text{NaOEt})}{(\text{alc})} \qquad \text{(Eq. 1)}$$

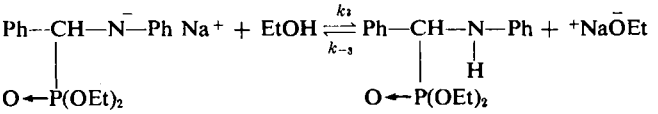
where $-d(SB)/dt$ is the rate of disappearance of the Schiff base; k_2, k_1, and k_{-1} are defined in Steps I and II (Scheme II); and (alc), (Schiff base), (phosphonate), and (NaOEt) represent the concentrations of these species. Since the alcohol concentration (alc) is constant, Eq. 1 is compatible with the observed third-order kinetics of the reaction (Table II). The Hammett plot (Fig. 1) provides additional support for the mechanism. At 30, 40, and 50°, the ρ-values for the reaction of 1.365, 1.368, and 1.349, respectively, were identical within experimental error. The positive ρ indicates the reaction would be favored by electron-withdrawing substituents on the *para*-position of the benzylidene moiety.



(Step I)



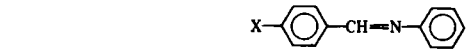
(Step II)



(Step III)

Scheme II—Proposed mechanism for nucleophilic addition of diethyl phosphonate to benzylideneaniline (Ph = phenyl)

Table II—Third-Order Rate Constants for Nucleophilic Addition of Diethyl Phosphonate to Various *p*-Substituted Benzylideneanilines[a]



Substituent X	Temperature[b] 303	313	323
NMe_2	$(2.380 \pm 0.003) \times 10^{-3}$	$(3.833 \pm 0.005) \times 10^{-3}$	$(1.084 \pm 0.058) \times 10^{-2}$
H	$(2.933 \pm 0.170) \times 10^{-2}$	$(5.686 \pm 0.031) \times 10^{-2}$	$(9.666 \pm 0.100) \times 10^{-2}$
Cl	$(6.966 \pm 0.017) \times 10^{-2}$	$(1.041 \pm 0.032) \times 10^{-1}$	$(2.394 \pm 0.192) \times 10^{-1}$

[a] The rate constants are based on a minimum of 12 runs and are in units of $l.^2\ m.^{-2}\ sec.^{-1}$. The standard deviations are derived from the least-squares plot. [b] The temperature is in degrees absolute.

In the rate-determining step, Step II, any factor which reduces the electron density on the carbon of the carbon–nitrogen double bond would facilitate the attachment of the negatively charged phosphonate anion. The proposed mechanism predicts the positive ρ-value obtained experimentally.

The activation parameters were somewhat surprising since these values (Table III) indicated the reaction was controlled by the entropy of activation rather than by the enthalpy. Previously, Weinstein and McIninch (3) reported the effect of *para*-substituents on the base strength of benzylideneanilines. They observed a correlation between base strength and σ^+; however, ΔH^0 was not proportional to electron withdrawal, but a correlation between ΔS^0 and electron-withdrawing power was observed. Thus, we are not unique in observing entropy-controlled reactions. Entropy control of the reaction could be rationalized if the transition state (Scheme III) forms in such a manner that the factor which changes with the various Schiff bases is the degree of localization of the negative charge of this transition state. The difference in charge localization will change the solvation of the transition state, resulting in a change in the entropy of activation. It is not unreasonable to expect this change to be proportional to the change in the Hammett value and to observe a linear Hammett plot.

EXPERIMENTAL

Preparation of Reagents—Absolute ethanol (4) was prepared by refluxing for 2 hr. 1 l. of commercial absolute ethanol, 7 g. of metallic sodium, and 30 ml. of diethyl phthalate. The ethanol was then distilled through a vigreux column into a carefully dried flask. The diethyl phosphonate was prepared by carefully fractioning the commercial product and selecting only the center 50% for further use. A portion of this center fraction was freshly distilled for each day's run. The benzylidineaniline was prepared by reacting the appropriate benzaldehyde with aniline (5). The products were recrystallized until a constant melting point was reached. The melting points and the UV spectra of these compounds agreed with the values reported in the literature (6).

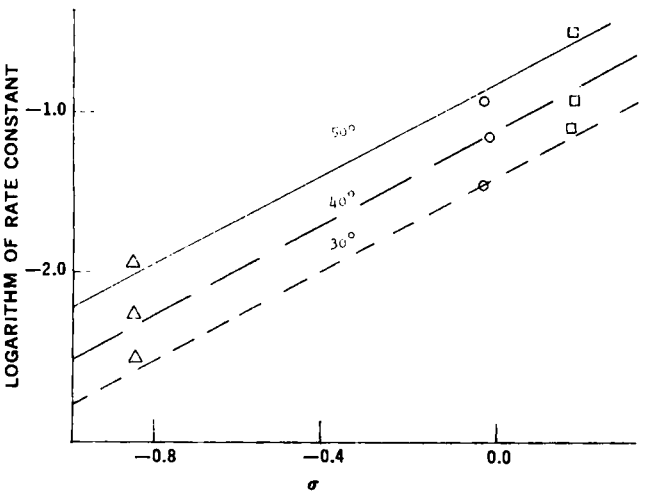


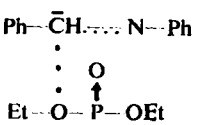
Figure 1—*Hammett plot for the nucleophilic addition of diethyl phosphonate to various substituted benzylideneanilines. Key:* △, *p-dimethylaminobenzylideneaniline;* ○, *benzylideneaniline; and* □, *p-chlorobenzylideneaniline.*

Measurement of Absorptivities—The spectra were measured at 10-nm. intervals from 220 to 400 nm. with a spectrophotometer[1]. The molar absorptivities were obtained by means of a computer program which converted percent transmission to absorbance and determined the slope of the line obtained by plotting absorbance against molar concentration. The slope was obtained by a standard least-squares procedure.

Preliminary Runs—The wavelength at which the reaction was to be observed was selected by following the reaction at several wavelengths. The lowest wavelength at which the absorbance had a negligible value at the completion of the reaction was selected for further determinations. The addition product of the benzylideneaniline and diethyl phosphonate was prepared, and the spectrum of the addition compound and the spectrum of the preliminary run were compared. In no case were any significant differences noted. The comparison demonstrated that the addition compound was the only spectrally detectable product.

Determination of Rate Constants—Extreme care was exercised in excluding contamination from moisture. All flasks were flame dried under dry nitrogen. Volumetric flasks were sealed with multiple-dose rubber stoppers, and all sampling was carried out by means of a syringe which had been flushed with dry nitrogen. A stock solution of benzylideneaniline was prepared in absolute ethanol. A dried volumetric flask was partially filled with absolute alcohol, and a carefully weighed piece of sodium was added. The flask was protected from the atmosphere by a drying tube while the sodium was dissolving. After the sodium dissolved, the flask was sealed and placed into the water bath to equilibrate. After 1 hr. the flask was removed and, as quickly as possible, the cap was removed and the appropriate amounts of benzylideneaniline stock solution and diethyl phosphonate were pipeted into the flask, the solution was brought to volume, and the flask was shaken. A sample was removed with a syringe, and the flask was placed into the water bath.

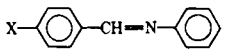
The first sample served as a check on the initial concentration of Schiff base. At periodic intervals, a sample was removed from the flask by means of the syringe and the percent transmission and sample time were recorded. The reactions were normally followed to from 80 to 90% completion. The pseudo-first-order rate constants were determined by means of a computer program which converted transmittance into absorbance and then computed the rate constant at each point. The program also computed the least-squares rate constant by standard statistical procedures, and the least-squares rate constant was used for all further calculations. The pseudo-second-order rate constants were obtained by determining the slope of the least-squares line obtained by plotting the pseudo-first-order rate constant *versus* sodium ethoxide concentration. The third-order rate constant was obtained from the slope



Scheme III—Transition state for nucleophilic addition of diethyl phosphonate to benzylideneaniline

[1] Beckman DU.

Table III—Activation Parameters for Addition of Diethyl Phosphonate to Substituted Benzylideneanilines



Substituent X	E_a, kcal.	ΔS^{303}, e.u.	ΔS^{313}, e.u.	ΔS^{323}, e.u.
NMe_2	11.29	−23.3	−22.4	−20.4
H	11.30	−18.3	−17.1	−16.1
Cl	11.61	−16.6	−15.9	−14.3

of the line obtained by plotting the pseudo-second-order rate constant *versus* diethyl phosphonate concentration.

At least four runs were made at each diethyl phosphonate concentration and three diethyl phosphonate concentrations were used, making a minimum of 12 runs for each rate constant. The third-order rate constants with the appropriate standard deviations are summarized in Table II.

Determination of Activation Parameters—The activation parameters were calculated by means of two computer programs. The slope of the Arrhenius plot was obtained by means of the normal least-squares computation, and this slope was used to calculate the heat of activation. The entropy of activation was computed by means of a second computer program using the usual equations. The results are shown in Table III.

Determination of Hammett ρ-Constants—The values of the log of the rate constants and standard Hammett σ-constants were supplied to a computer program which calculated the slopes by a normal least-squares method.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 26, 1971, from the *College of Pharmacy, North Dakota State University, Fargo, ND 58102*

Accepted for publication September 7, 1971.

Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

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Drug Transport VI: Functional Integrity of the Rat Everted Small Intestine with Respect to Passive Transfer

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Abstract □ Mucosal-to-serosal flux of a number of solutes across the rat everted small intestine was determined as a function of time. Certain compounds including aniline, benzocaine, salicylamide, and antipyrine, which demonstrated initial clearance values of >1 ml./hr., showed little change in permeability over the entire 2-hr. period of study under the experimental conditions. On the other hand, the transfer rates of compounds which were initially cleared at substantially lower rates, such as pralidoxime, riboflavin, methyl orange, eosine blue, and bromthymol blue, increased markedly and continually during the time course of the experiment. Determination of drug transfer rates after the intestine was incubated in buffer revealed that the marked increase in the clearance of these polar compounds with time is due, in part, to a loss of functional integrity of the preparation. The permeability of the everted intestine with respect to riboflavin and methyl orange increased by a factor of about two after only 30 min. of incubation in drug-free buffer solution.

Keyphrases □ Flux, mucosal to serosal—determined for solutes as a function of time, rat everted small intestine □ Drug transfer rates—variability over time, rat everted small intestine □ Drug transport—functional integrity, rat everted small intestine, passive transfer □ Everted small intestine, rat—functional integrity with respect to passive transfer

The everted gut technique for studying intestinal absorption was first introduced in 1954 (1) and since that time has found wide application, particularly in elucidating the transport mechanisms for various nutrients and physiologic substrates (2–4). More recently, the technique has been employed to study the influence of various factors on drug absorption (4). Its use as a potential screen for the absorption characteristics of new drugs has also been considered (5). Despite the widespread and continuing interest in this isolated preparation, there is comparatively little information regarding its functional and structural integrity. Although there are few studies in the area, there is nevertheless strong evidence that the intestinal preparation is "viable" with respect to certain metabolic processes and active transport mechanisms for several hours after removal from an intact blood supply. Bramford (6) found that the rate of oxygen consumption by isolated ileal and jejunal segments of 18-day-old rats was essentially invariant over 3 hr. Similar findings were reported by Jordana and Ponz (7) using intestinal segments from adult rats. These workers also