A STUDY OF KINETICS AND MECHANISM OF AQUEOUS AND ACID-CATALYZED HYDROLYSIS OF DIETHYL BENZOYLPHOSPHONATE BASED ON ^{31}P NMR, RAMAN, AND ULTRAVIOLET SPECTROSCOPIC ANALYSIS

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A STUDY OF KINETICS AND MECHANISM OF AQUEOUS AND ACID-CATALYZED HYDROLYSIS OF DIETHYL BENZOYLPHOSPHONATE BASED ON ^{31}P NMR, RAMAN, AND ULTRAVIOLET SPECTROSCOPIC ANALYSIS

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF PLATES

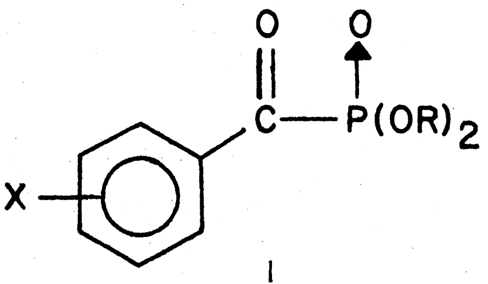
Plate Page

CHAPTER I

HISTORICAL

Acylphosphonates

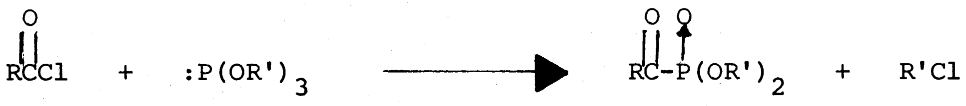
Acylphosphonates are phosphorus esters in which two strongly electron-withdrawing groups (carbonyl and phosphonyl groups) are directly attached to each other as in 1. In these systems, unlike the carbon analogs[44] (the α-dicarbonyl compounds), the dihedral angle between the carbonyl and the phosphonyl groups is believed to be approximately 90° in the most stable conformer.[25,26] Acylphosphonates also have considerable toxicity although the mode of biological activity is not fully understood.[58] Preliminary studies [94] on diethyl benzoylphosphonate (1a) (X = H, R = Et) showed possible immunostimulation in cancer therapy in mice.



1

Since 1972, when the literature on acylphosphonates was reviewed by Clark,[25] a large number of papers on this family have been published. The first section of this review will cover the literature published from 1972 to 1977, although a few earlier papers, not included by Clark[25] but pertinent to this work, will be cited.

The Michaelis-Arbuzov rearrangement is still the most widely used method for the synthesis of these esters. A Russian review on the



$$R\overset{O}{\overset{\|}{C}}Cl \quad + \quad :P(OR')_3 \longrightarrow R\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\uparrow}{P}}(OR')_2 \quad + \quad R'Cl$$

Arbuzov reaction and its development has been published.[72] An interesting example reported very recently[59] for application of the Arbuzov reaction is the preparation of a novel ester shown in the following reaction.

$$(OCN)_2\ddot{P}(OEt) + Cl_3CC(O)P(O)(OR)_2 \xrightarrow{20-75°} (OCN)_2P(O)(CCl_2)C(O)P(O)(OR)_2 + EtCl$$

The R represents an alkyl group. Many other examples exist in the literature.

Reactions

Acylphosphonates are an extremely reactive class of phosphorus esters. For example, fast nucleophilic substitution occurs which involves C-P bond cleavage. To illustrate the latter, hydrolytic reactions of acylphosphonates were first investigated by Ackerman and coworkers in 1956.[1] The R represented a long chain alkyl group while R'

$$RC(O)P(O)(OR')_2 + H_2O \xrightarrow[\text{Dioxane}]{93°C} RCO_2H + HP(O)(OR')_2$$

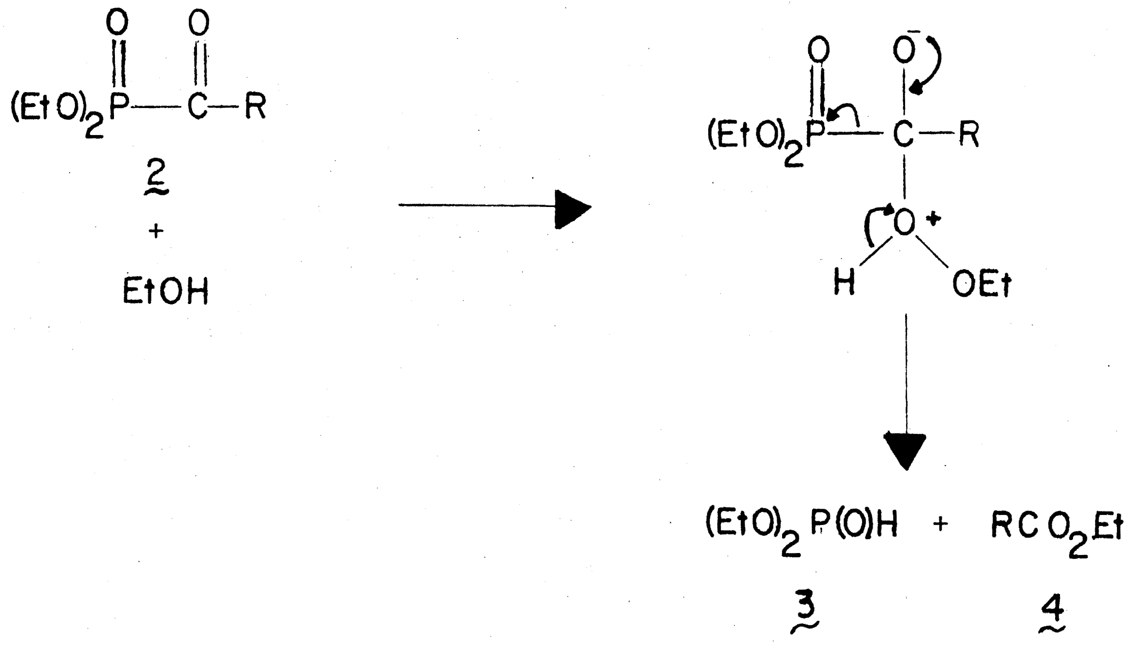
was Et (C_2H_5), *n*-Bu (*n*-C_4H_9), and others. No mechanism was discussed, however.

Nucleophilic attack of $\ddot{N}H_3$ on diethyl acylphosphonates was reported[84] to yield (85-90%) the corresponding amide and diethyl hydrogenphosphonate (**3**). Reaction of EtOH with diethyl acylphosphonates,

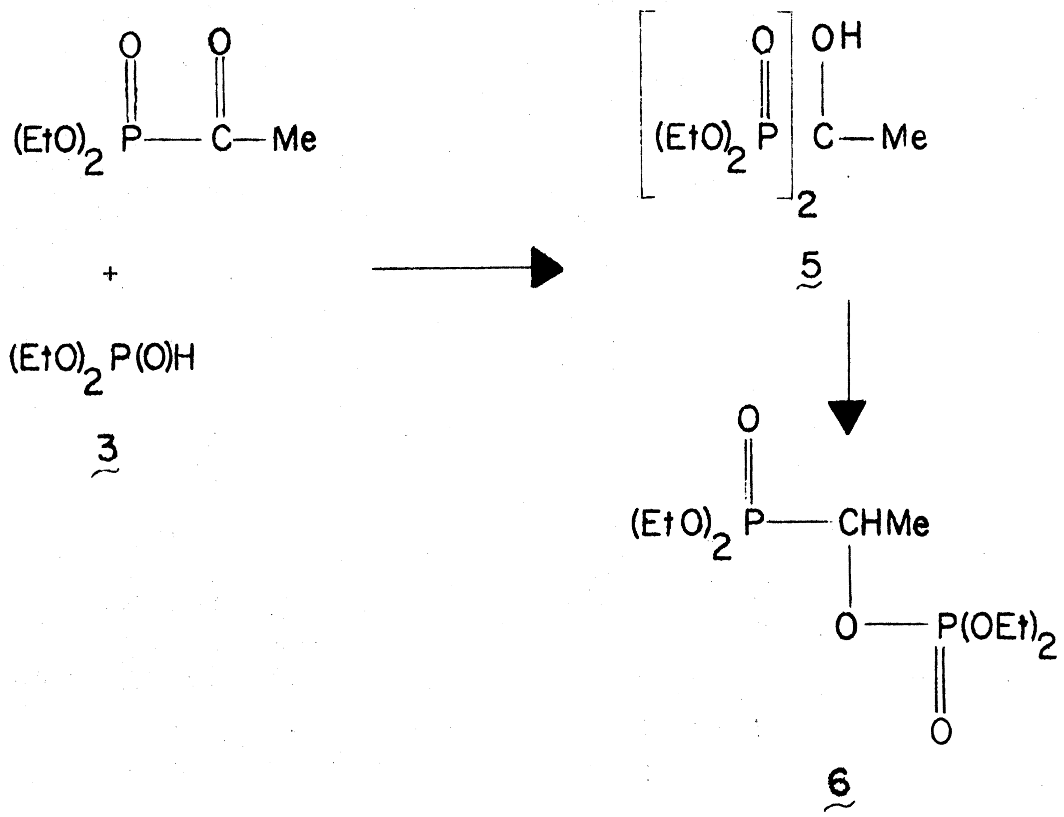
$$\underset{\underset{\sim}{2}}{RC(O)P(O)(OEt)_2} + \ddot{N}H_3 \longrightarrow RC(O)NH_2 + \underset{\underset{\sim}{3}}{HP(O)(OEt)_2}$$

R = Me (CH_3), Et (C_2H_5), *n*-Pr (*n*-C_3H_7) or Ph (C_6H_5)

$RC(O)P(O)(OEt)_2$, in the presence of a basic catalyst or under the influence of heat, was observed[70] to yield **3** and ester **4** in which R = Me, *i*-Bu and Ph, etc.; the following mechanism was suggested:



Interestingly, an unusual side reaction was noted[70] in the case where R = Me. Starting with equimolar proportions of ethanol and diethyl



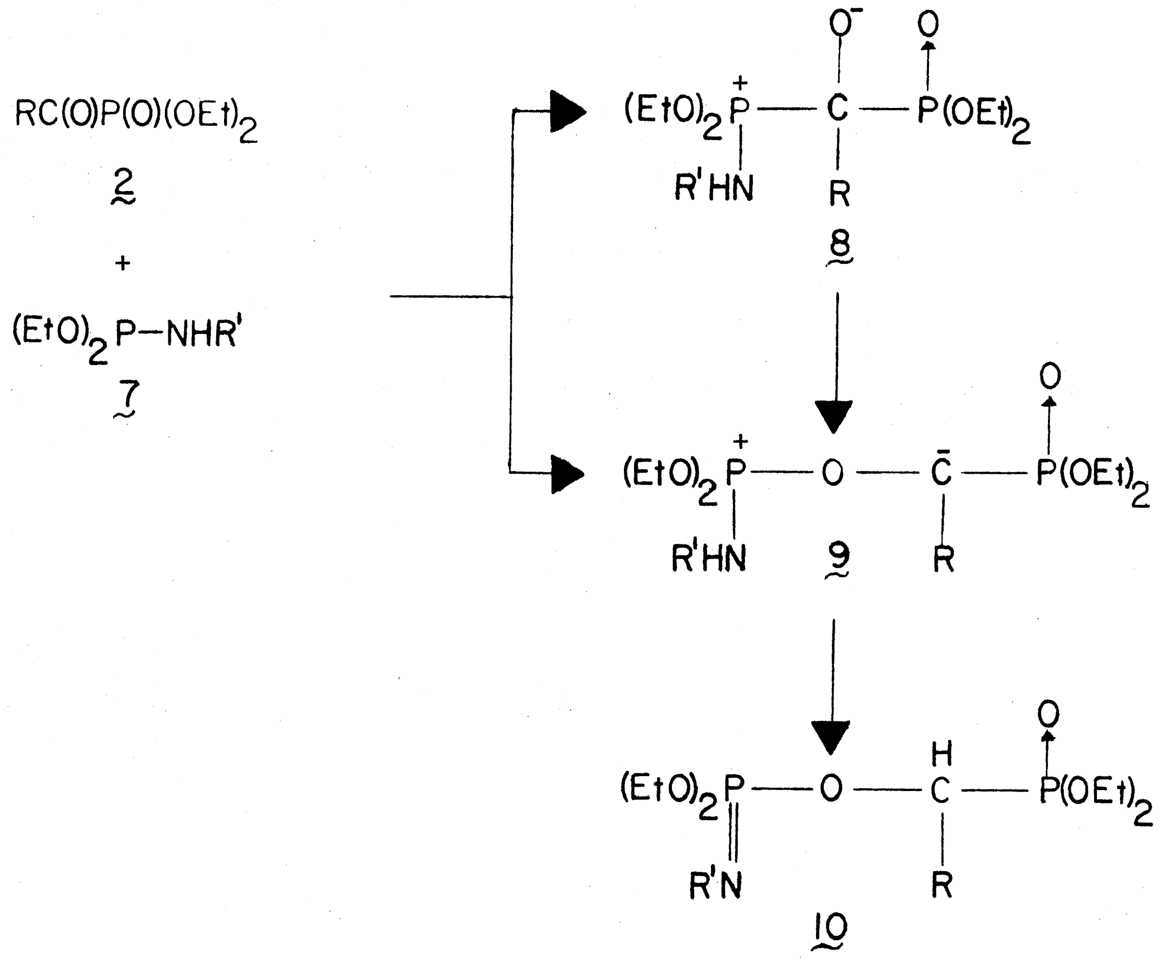
acetylphosphonate, the Russian workers[70] were able to isolate ester 6, supposedly produced from phosphonate-phosphate rearrangement of the intermediate 5.

Several nucleophilic-type reactions involving dimethyl benzolyphosphonate and secondary amines in the presence of $MgBr_2$ and with bromomagnesium derivatives of several amines have been also described.[82] The reactions are classified under two categories: (a) a direct benzoylation reaction in which the dimethylphosphite group was lost and (b) reactions in which a stable, substituted dialkyl α-hydroxybenzylphosphonate was formed.

Synthesis of α-aminophosphonic acids has been accomplished by two different groups of workers[4,13,15] starting from the acylphosphonates.

The methods involve reduction of the corresponding oxime with Al-Hg in H_2O-EtOH[13,15] or with H_2/Raney-Ni[4] followed by hydrolysis of the phosphonyl ester group via aqueous hydrochloric acid.

Amides of tervalent phosphorous acids are known to give 1:1 addition products with acylphosphonates. For example, diethyl phenyl- and diethyl acetylphosphoramidites, on heating with diethyl acetyl- or diethyl benzoylphosphonate, gave the corresponding phosphorimidate 10.[71] The structures of the products were confirmed from a study of the IR, ^1H NMR and ^{31}P NMR spectra of the reaction mixture and also by chemical

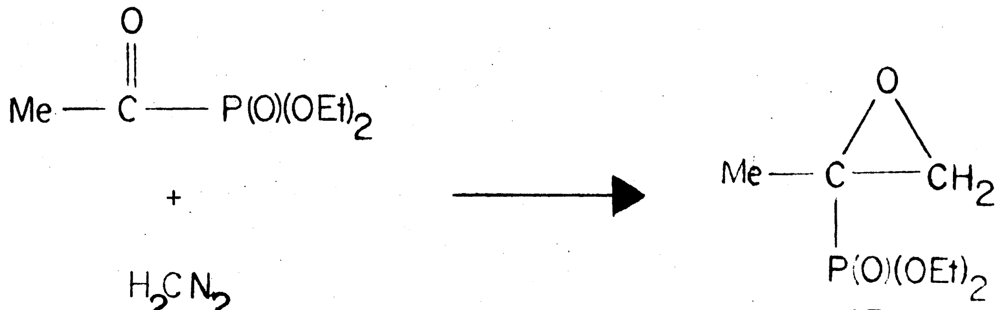


R = Me, Ph; R' = Ph, $CH_3C(O)$

degradation. The suggested mechanism included initial attack by the phosphorus atom in 7 on the carbonyl group in 2 to give a dipolar ion 8 which, on rearrangement, could give the second dipolar ion 9. In 9, migration of the proton on nitrogen (i.e., H on the NH group) to the electron-deficient carbon atom could occur to give product 10. The authors[71] also postulated that the phosphorus atom in 7 could directly attack the electron-deficient oxygen atom of the carbonyl group in 2 to give 9.

Reaction of acylphosphonates with diethyl phosphorisocyanatidite (11) has been reported[60,61] to give a mixture of the three isomers 12, 13, and 14 as evidenced by the TLC analysis and IR spectral data. In the proposed mechanism, formation of a dipolar ion by the initial attack of 11 on the acylphosphonate was suggested to be involved. This step could be followed by ring closure as shown on page 7.

Reaction of azo compounds with acylphosphonates has been a subject of recent interest. Arbuzov[3] reported that diazomethane reacted with diethyl acetylphosphonate to yield mainly diethyl 1,2-epoxy-2-propylphosphonate (15). Reaction of diazomethane with 1a has been recorded[3,62] to give phenacylphosphonate (16) in high yield (90%).[62]



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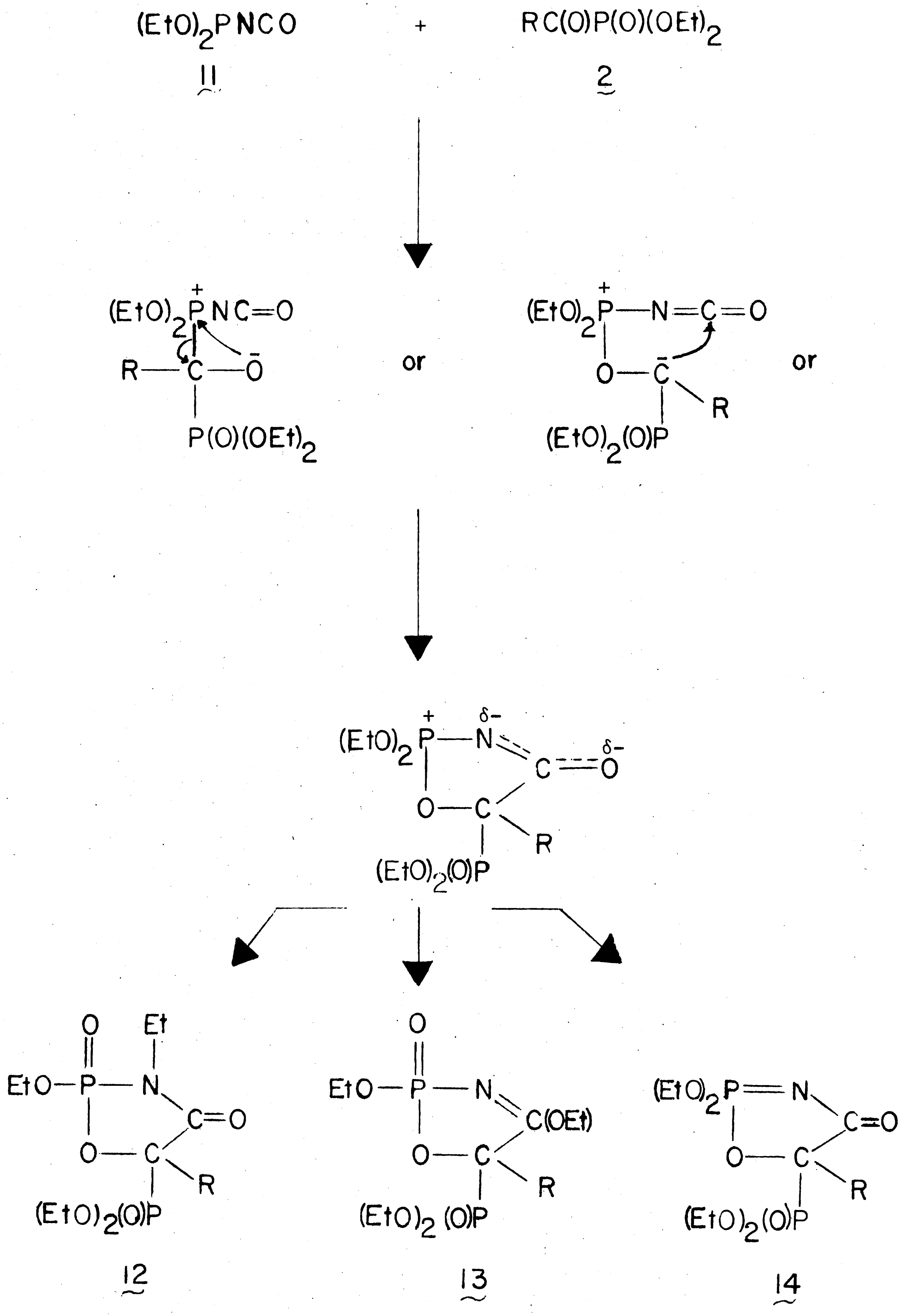
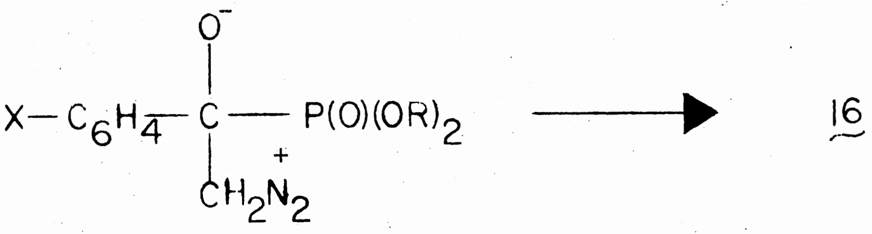

(EtO)2PNCO
+
RC(O)P(O)(OEt)2
11
2
or
or
12
13
14

$$\underset{\textbf{1a}}{PhC(O)P(O)(OEt)_2} + CH_2N_2 \xrightarrow[0°C]{\text{ether}} \underset{\textbf{16}}{PhC(O)CH_2P(O)(OEt)_2}$$

The mechanism is believed to proceed via an intermediate dipolar ion **17a** followed by migration of the dimethoxyphosphonyl group to the electron deficient methylene carbon atom. Kost and co-workers[19] further investigated the ease of migration of the diethoxyphosphonyl group or dimethoxyphosphonyl group as compared with the phenyl and certain substituted aryl groups (*m*-ClC_6H_4 and *p*-$MeOC_6H_4$) in **17**. It was discovered that the dialkoxyphosphonyl group migrated preferentially even when compared to the *p*-anisyl group in the intermediate dipolar ion **17**.



17

17: a. X = H, R = EtO; b. X = *m*-Cl, R = Me; c. X = *p*-MeO, R = Me.

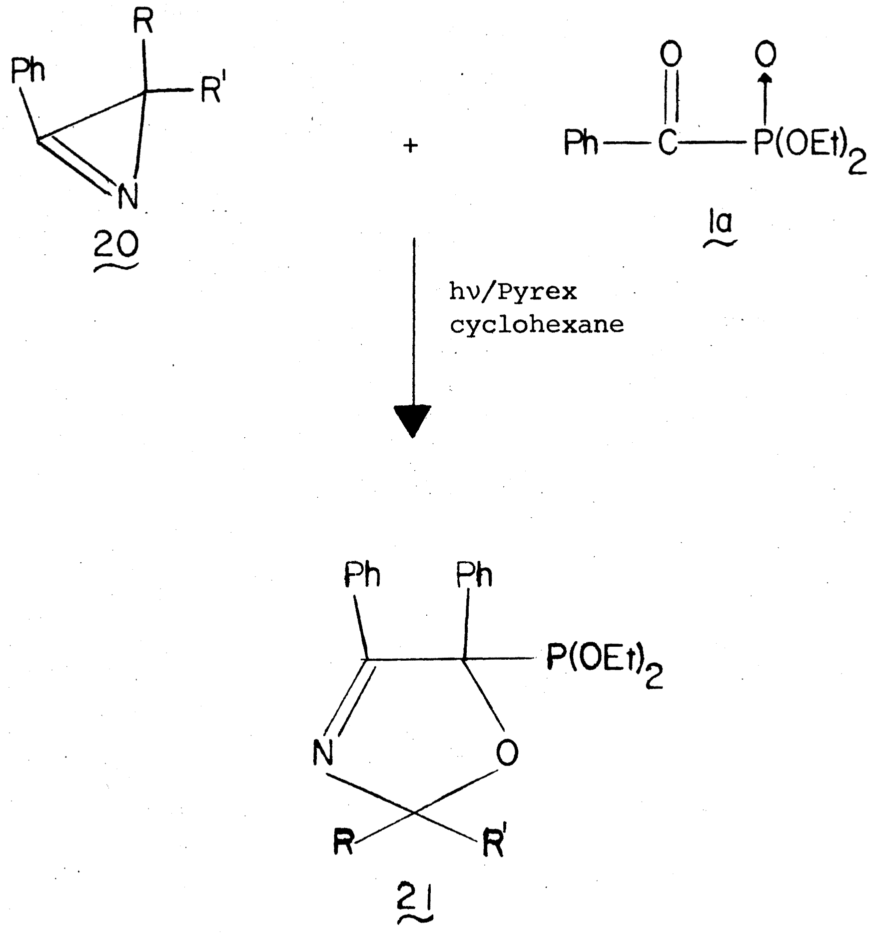
According to a group of Russian workers,[40] the reaction of CH_2N_2 on dialkyl acylphosphonates not only produced the compounds containing an inserted CH_2 group (as in **18**) as described earlier but also gave the methoxy compound **19**. The structure elucidation of **19** has not appeared.

$$R(R'O)P(O)C(O)C_6H_4R''\text{-}\underline{p} \xrightarrow{CH_2N_2} \underset{\textbf{18}}{R(R'O)P(O)CH_2C(O)C_6H_4R''\text{-}\underline{p}}$$

$$\textbf{18} \xrightarrow{CH_2N_2} \underset{\textbf{19}}{R(R'O)P(O)CH{=}C(OMe)C_6H_4R''\text{-}\underline{p}}$$

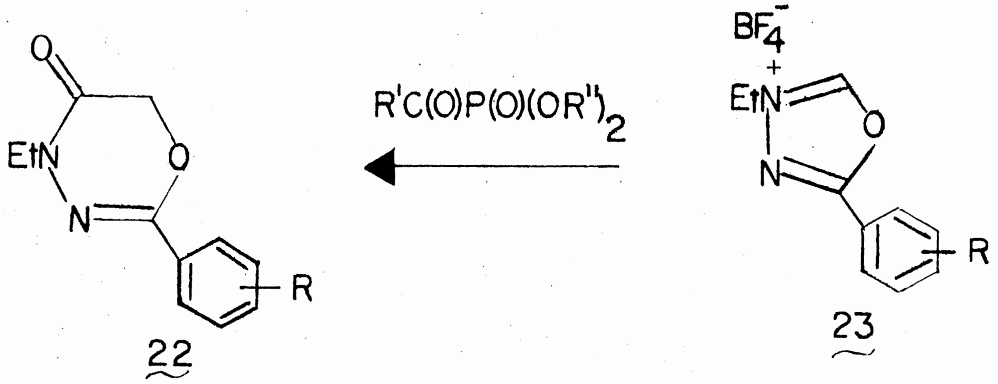
R:	MeO	Ph	MeO	Me
R':	Me	Me	Me	Me
R":	H	H	Me	H

Cycloaddition of 2-substituted, 3-phenylazirines 20a-c with the C=0 group in 1a via irradiation (with a high pressure mercury lamp) of a solution of the two reactants in cyclohexane has been described.[39] The product was identified as 21 based on spectral analysis.



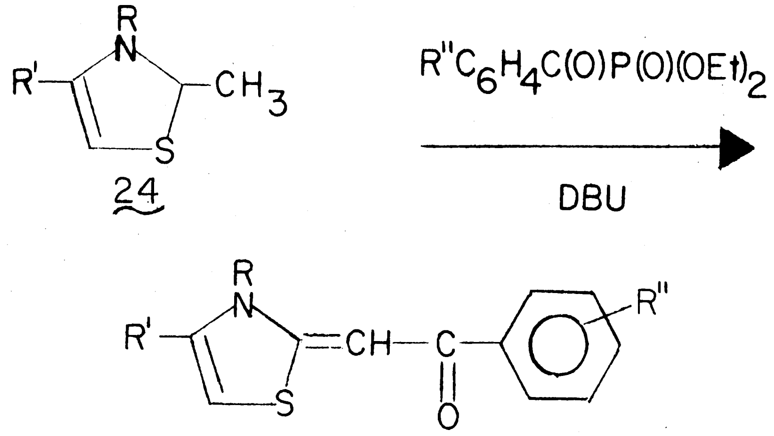
a: R = R' = Me; b: R = H, R' = Ph; c: R = H, R' = Me.

Takamizawa and co-workers[89] developed a novel synthetic procedure for obtaining 1,3,4-oxadiazin-5-one derivatives 22 from 1,3,4-oxadiazolium salts 23 by reaction of the latter with acylphosphonates in presence of triethylamine. Although the final product does not contain the phosphorus moiety, an acyclic intermediate containing phosphorus was reported. A definite mechanism remains obscure, nevertheless.



R = H, *o*-MeO, *p*-Cl; R' = Ph, $PhCH_2$, *p*-ClC_6H_4, *p*-MeC_6H_4, *p*-*n*-PrC_6H_4, *p*-$MeOC_6H_4$; R" = Me, Et.

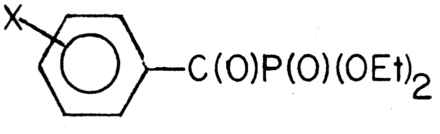
A general method for the acylation of 2-methylthiazolines 24 by reaction with acylphosphonates in presence of 1,5-diazabicyclo[5.4.0]-undec-5-ene(DBU) has been discussed in the preparation of 32 different compounds.[86] Similar reactions of acylphosphonates with substituted 2-methyl benzimidazolium salts have also been observed.[88]



R = Me, CH_2Ph, etc., R' = H, Me; and R" = H, *p*-F, *p*-Cl, *p*-Br, *p*-Me, *p*-OMe *m*-Br, *m*-Me, *o*-Me, *o*-OMe.

Physical Properties and Molecular Structure

A variety of acylphosphonates $RC(O)P(O)(OR')_2$, in which R = alkyl or aryl group and R' = Me, Et, *i*-Pr, etc., have been synthesized. Moreover, physical and spectral characteristics of these esters have been analyzed both by the group in this laboratory[12,14,15,17,26] and by others.[54,56,74,81,92] On the basis of IR and ^1H NMR,[12,14,17] and UV[12,56,81,92] spectral analysis on many dialkyl *p*-substituted aroylphosphonates 1 (shown below), the following results and conclusions have been evaluated for systems where X = H, *p*-F, *p*-Cl, *p*-Br, *p*-Me, *p*-*t*-Bu,



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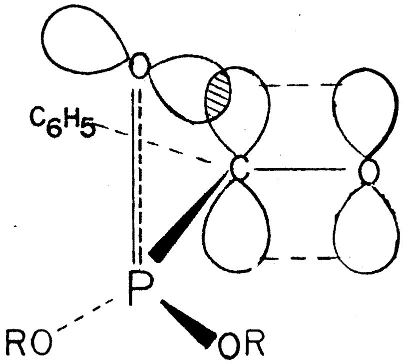
p-OMe; and R = Me, Et, *i*Pr, *n*-Bu, and alkyl groups. These compounds normally have two characteristics UV absorption bands: a) with

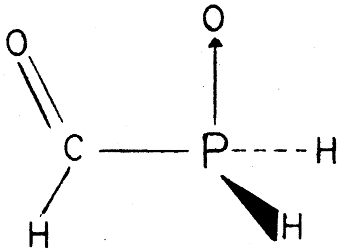
λ_{max} = 258-295 nm and log ε_{max} = 4.05-4.31 corresponding to a $\pi \rightarrow \pi^*$ transition and b) the second band with λ_{max} = 373-385 nm and log ε_{max} = 1.91-2.18 corresponding to an $n \rightarrow \pi^*$ transition. Both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ bands exhibit a bathochromic shift of 17 to 30 nm as compared to the corresponding substituted benzaldehydes. A linear correlation exists between λ_{max} for the $n \rightarrow \pi^*$ band and the Hammett σ constant for the p-substituted benzoylphosphonates 1 with the following substituents on the arene ring (para): X = OMe, t-Bu, H, Cl and Br and R = Et[92] and (para) X = H, Me, F, Cl, Br, OMe and R = Et.[81] A linear correlation between $(\lambda_H - \lambda_X)/\lambda_H$ and σ values for X(p) = OMe, Me, H, Br and Cl has been reported.[56] From the IR spectra of several aroylphosphonates 1 (X = H, p-OMe, p-Cl, o-Cl, p-t-Bu, and R = Me; and X = p-OMe, and R = Et, i-Pr, and n-Bu),[17] the C=O absorption was found to be in a low range (1639-1672 cm^{-1}) as compared with that in the α-diketones (1710-1730 cm^{-1})[17] and the corresponding aryl aldehydes (1695-1715 cm^{-1}).[17] The above observations would suggest an alteration of the electronic ground state of the carbon-oxygen bond. Model A shows orbital overlap to provide conjugation between the C=O and P→O groups.[17] The filled nonbonding orbital of oxygen of the phosphonyl groups could interact with π-orbital of the



Model A

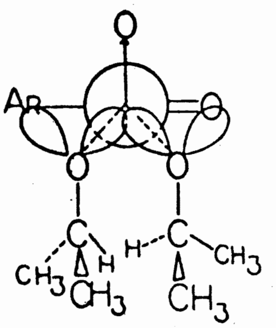
carbon atom of the carbonyl group. Assuming sp^2-hybridization on oxygen of the phosphonyl group, overlap of the type illustrated has been suggested to be maximum when P→O bond is perpendicular to the plane composed of aryl ring, carbon, and phosphorus atom.[17]

Interestingly, the results of an extended Huckel calculation performed[26] on model structures of acylphosphonates like Model B (in which the substituent groups were replaced by hydrogen atoms) indicated lowering of potential energy by 7 ev when d-orbitals of the phosphorus atom were included. This supports the postulation of 2 pπ-3 dπ type interaction in acylphosphonates. Furthermore, computation of potential energy for the model system B as a function of the OPCO dihedral angle showed a minimum, when the dihedral angle was about 90° even though the difference in the potential energy between the conformer with angle OPCO (θ) = 0° or 180° and that conformer with angle θ = 90° was only of the order of 0.05-0.08 eV.

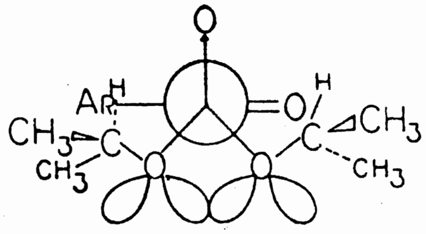


Model B

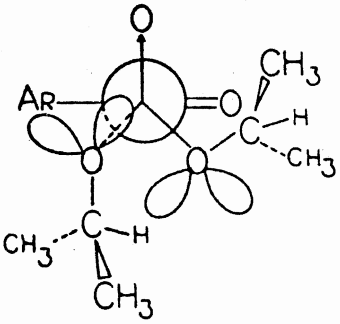
Calculation of dipole moments for conformations 25a-d for various dihedral angles θ were performed on several diisopropyl aroylphosphonates.[26] The following observations were made from such calculations. Different combinations of angle θ and ester group orientations gave



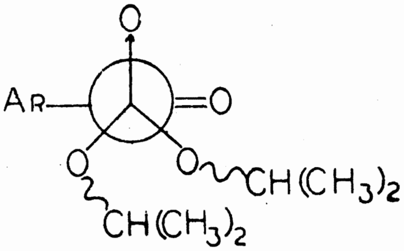
Conformation 25a



Conformation 25b



Conformation 25c



Conformation 25d

Conformations 25a-d for Diisopropyl Aroylphosphonate values of dipole moments comparable to the experimental values (see Table I). The dependence of molecular dipole moment on the size of angle θ is apparently much more significant compared to the dependence upon the ester group orientation. The best match of the experimental data (μ_{exp} ranges from 2.53 D to 3.20 D for most of the aroylphosphonates) was obtained[26] by considering different conformers all of which had a dihedral angle of approximately 90°.[26] Examination of ^{1}H NMR and ^{31}P NMR spectra of several disopropyl aroylphosphonates at variable temperatures indicated the presence of several rotational isomers also in solution.[26] Caution is needed for extrapolation of these data to the diethyl or dimethyl analogs, however, because these alkyl groups are smaller.

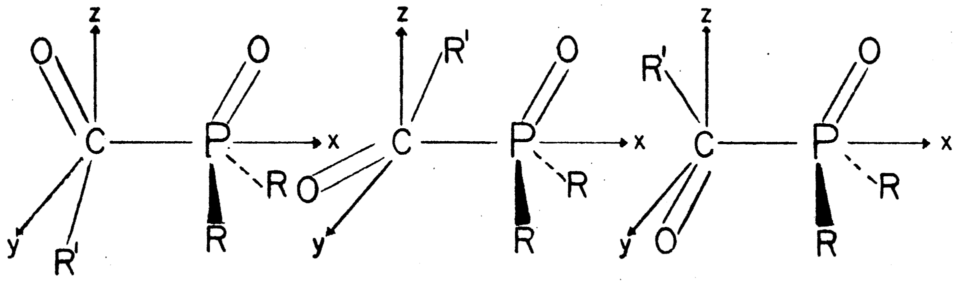
TABLE I

CALCULATED DIPOLE MOMENTS (DEBYE UNITS) FOR DIISOPROPYL AROYLPHOSPHONATES[25]

Dihedral Angle (θ)	Conformation **25a**	Conformation **25b**	Conformation **25c**	Conformation[a] **25d**
0.0	3.56	5.15	6.78	5.08
45.0	3.37	4.47	6.31	4.70
90.0	2.88	3.15	5.02	3.64
135.0	2.29	1.50	3.24	2.09
180	1.99	1.19	2.10	0.82

[a] Free rotation of isopropyl groups is assumed.

A group of Russian workers[54] calculated the conformer population ratios in certain acylphosphonates based on the experimentally measured dipole moments and values were calculated from the group moments (collected from the literature). A specific geometric model described below was employed. The authors assumed a OPCO dihedral angle of θ=0° for *syn* **26a** and θ = 180° for *anti* conformer **26c**.

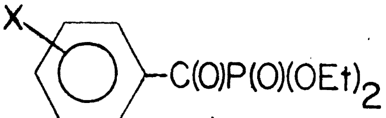


26a **26b** **26c**

θ = 0° θ = 90° θ = 180°

R = OEt, R' = R"-C_6H_4, and R" = H, *p*-Cl, *p*-Br, *p*-NO_2, *p*-OMe, *m*-Cl, *m*-Br, and *o*-Cl.

Considering as a specific example compound **1a**, a calculated value determined was μ_{syn} = 4.51 D and μ_{anti} = 0.50 D compared to μ_{exp} = 2.76 D. From the above values of dipole moments, the conformer ratio could be calculated to be 63% *trans*- and 37% *syn*-conformer. For the conformation **26b** in which the dihedral angle θ = 90°, μ_{cal} for **1a** should have a value between 0.50 D (μ_{anti}) and 4.51 D (μ_{syn}). On the basis of dipole moment studies on **1a** and other *p*-substituted acylphosphonates, the Russian authors[54] postulated the existence of a flat arrangement of the C(O)-P(O) group rather than an orthogonal arrangement. However, no NMR or any other type of analysis was performed to verify this hypothesis. Examination of both ^1H and ^{31}P NMR spectra of **1a-c** (compounds used in

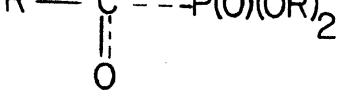


la-c

la, X = H; lb, X = p-Cl; lc, X = p-Me

this work) showed only the expected signals indicating that the process of exchange between rotational isomers was fast at room temperature on the NMR time scale and that the signals were the result of averaging with possibly several conformers.

An observation of the IR spectra for dimethyl acetylphosphonate and diethyl acetylphosphonate (with and without solvent) revealed a doublet for the C=O stretching frequency (1700, 1710 cm^{-1}).[74] The ratio of the intensities of the components of the doublets was found to change with solvent polarity and with temperature. No such doublet was observed in the case of la. From these results, it was tentatively concluded that in both dimethyl and diethyl acetylphosphonates a dynamic equilibrium existed between at least two rotational isomers[74] at room temperature. From a comparison of IR, ^1H, ^{31}P NMR, and UV spectral data of a few acylphosphonates, acylphosphinates and acylphosphine oxides, similar conclusions were reached, namely, that the C=O group probably participates in bonding with the 3-d orbitals of the phosphorus atom as represented by Model C[63].



Model C

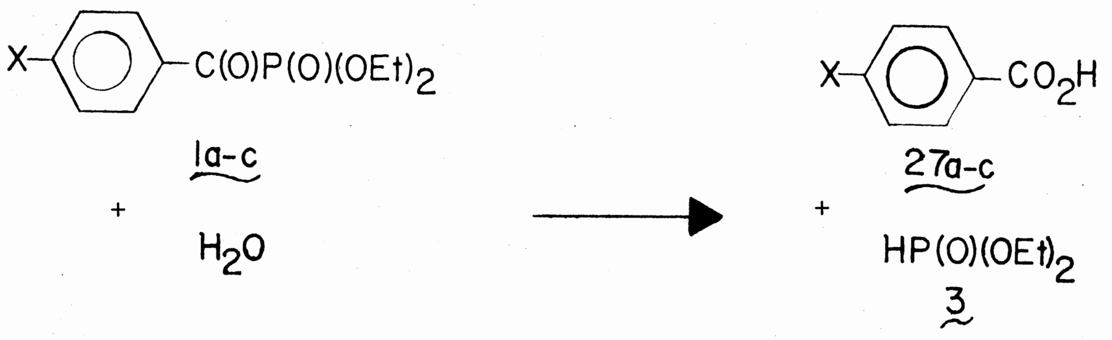
Polarographic studies on reduction of dialkyl aroylphosphonates have been reported by two different groups of workers.[16,79] The electron transfer process appears to proceed via acceptance of the first electron by the carbonyl group and, in the case of diethyl benzoylphosphonate, a ρ value of +4.7 for the $E_{1/2}$ was observed.[16]

Hydrolytic Reaction and Kinetic Studies

Ackerman and co-workers[1] noted that the acylphosphonates shown below underwent hydrolysis in dioxane-water mixture. They determined that the rate of hydrolysis, when measured by the total acidity of the solution as a function of time at 93°C, depended upon both the size of the acyl group and the size of the ester function attached to the phosphonyl group. The rate of hydrolysis was also observed to be slowed as the size of R and R' increased. No kinetic data or mechanism was

$$RC(O)P(O)(OR')_2$$

put forth, however. Fifteen years later, a detailed kinetic study appeared[56] focused upon the general base-catalyzed hydrolysis reaction of the following three *p*-substituted aroylphosphonates (1a-c).

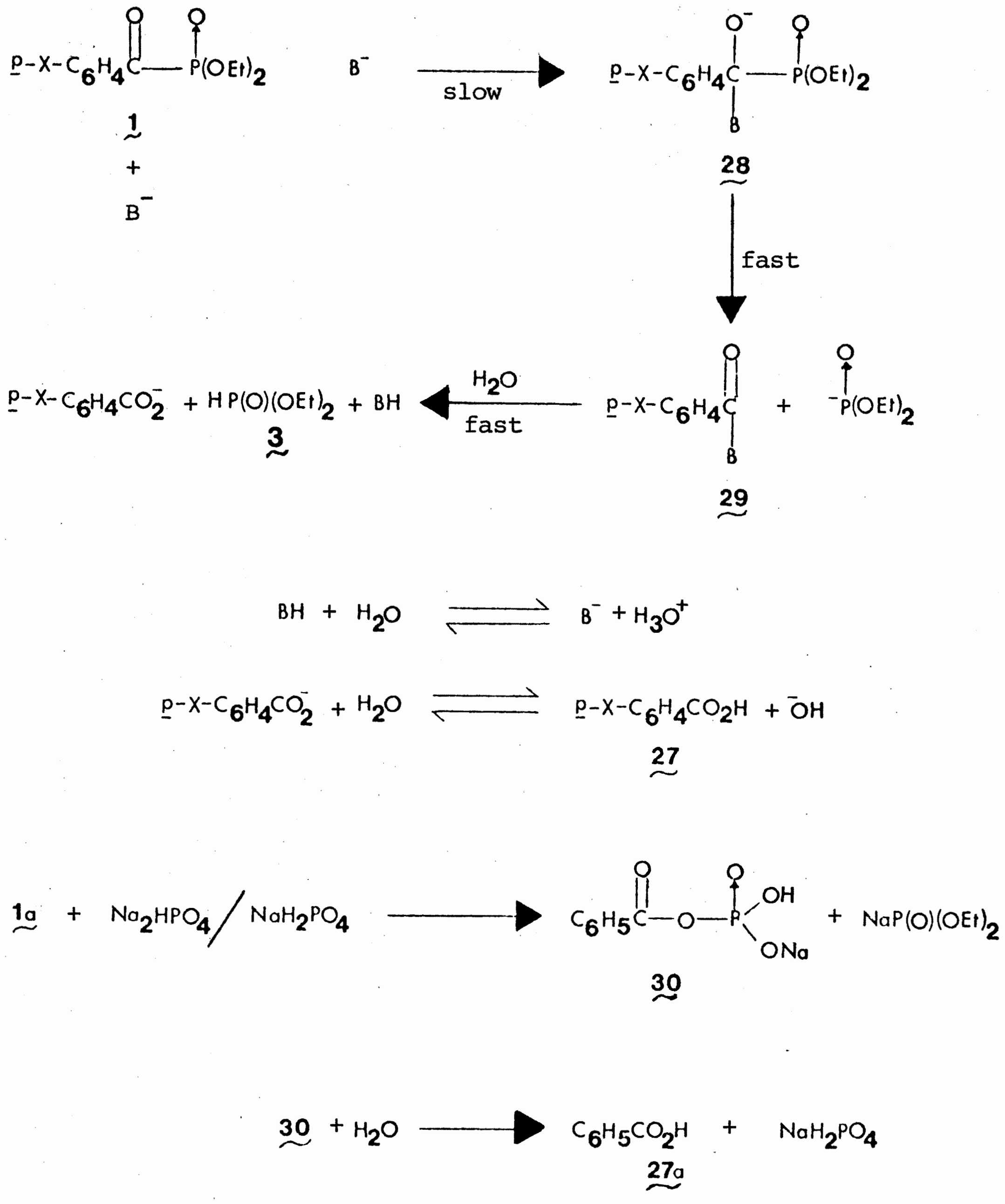


a. X = H; b. X = Cl; and c. X = Me

The reaction rates were measured by monitoring the disappearance of the $n \rightarrow \pi^*$ band (near 367 nm) of solution of ester **1a-c** in dioxane-phosphate buffer ($HPO_4^=/H_2PO_4^-$) medium. The results and conclusions are summarized below.

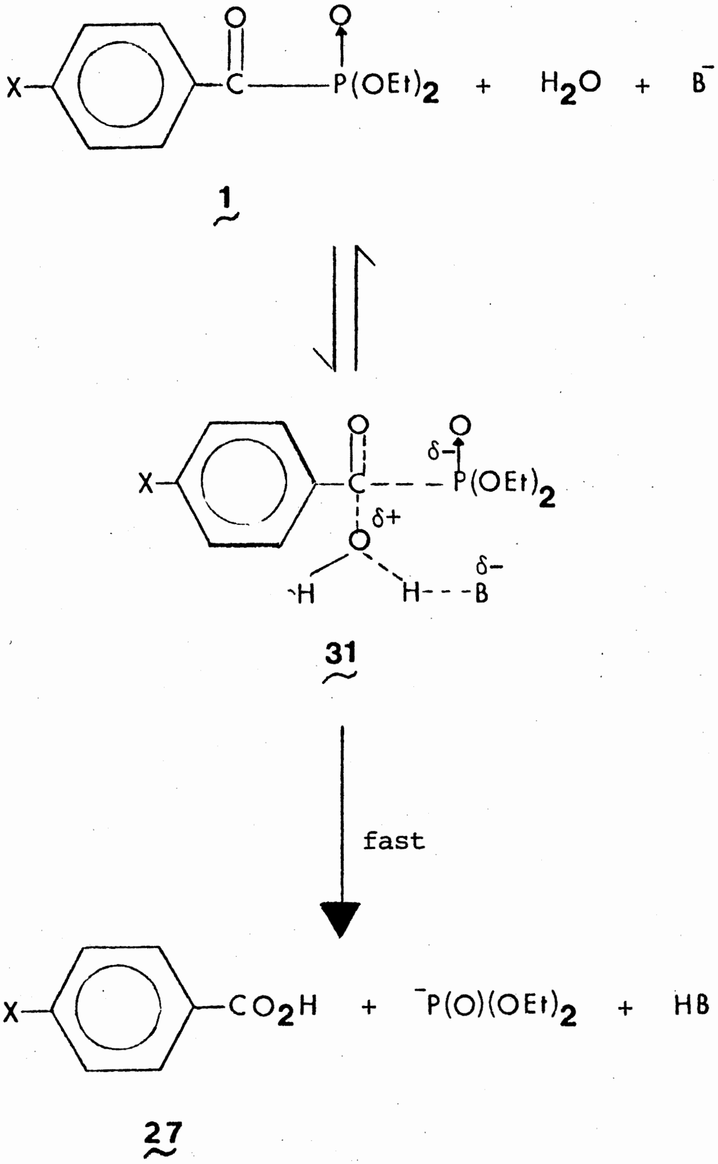
The reaction was found to be pseudo first-order in **1a-c** in the pH range (5-8) studied. Also, general base-catalysis [catalyzed by the $HPO_4^=$ (present in solution as a part of the buffer)] was observed, i.e., the pseudo first order-rate constant at constant pH was found to depend upon the concentration of $HPO_4^=$. Rate constants were noted to increase as pH was raised—typical of a base-catalyzed reaction. Rate constants were also found to increase with the dielectric constant of the medium (by varying the dioxane-buffer ratio from v/v 1:1 to 1:5). The determined $\Delta H^\ddagger$ and $\Delta S^\ddagger$ values were 12.4 kcal mol^{-1} and -35 eu, respectively, for the hydrolysis of **1a** at pH = 5 in v/v of 1:3 dioxane-buffer medium. A Hammett correlation was noted for the substituents used and ρ was reported as +2.20 at pH = 5.0 in v/v 1:3 dioxane-buffer medium. Two alternative mechanisms were proposed on the basis of the above results (Scheme I[56] and Scheme II[2]). In scheme I, the base participates as a nucleophilic catalyst. In the alternative mechanism according to Scheme II, the reaction is considered a general base-catalyzed reaction in which H_2O molecules directly participate in forming the transition state **31** in a termolecular rate-determining (r.d.) step. As a means of testing the two mechanisms, reaction rates were measured[2] (as reported in a subsequent paper)[2] in two different buffers (imidazole and phosphate) which had nearly the same basicity (pk_a = 6.95 and 7.21, respectively, at 25°C) but quite different nucleophilic properties.[2] The reported values of $k_{HPO_4^=}$ and k_{Im} were : 8.0×10^{-2} L mol^{-1} sec^{-1}

SCHEME I



where $B^- = {}^-OH$ or $HPO_4^=$; and **1**. a. X = H, b. X = Cl, c. X = Me.

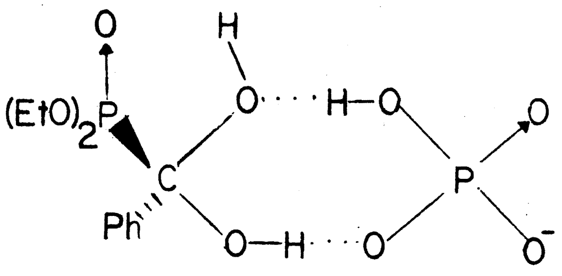
SCHEME II



where B^- = ^-OH or $HPO_4^=$.

and 7.2 x 10^{-2} L mol^{-1} sec^{-1}, respectively, at 20°C. This result is suggestive of Scheme II being operative. However, Scheme II would predict a high solvent isotopic effect from the rate determining step. The reported value for the solvent isotopic effect was $k_{HPO_4^=}$ / $k_{DPO_4^=}$ = 1.5 at pH = 7 at 20°C and in v/v 1:4 dioxane buffer medium.

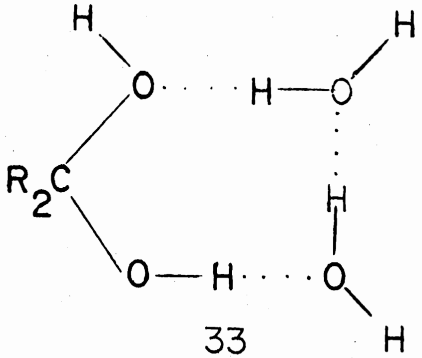
The low solvent isotopic effect and the kinetic results reported[2,56] for the base-catalyzed hydrolysis of 1a could be better explained by a modified structure for the transition state. In the modified mechanism, 1a is assumed to form an unstable cyclic intermediate 32 with one molecule of H_2O and one molecule of the base in the r.d. step. This is followed by a fast intramolecular proton abstraction (see Scheme VI, page 68 in Discussion section).



32

According to Scheme I, for the hydrolysis of 1a in phosphate buffer $HPO_4^=$ / $H_2PO_4^-$ (Na salt) in aqueous medium [where $HPO_4^=$ (Na salt) would act as a general base], the intermediate benzoylphosphate 30 would be a relatively stable species. The half life for the hydrolysis of 30 (to benzoic acid and phosphate salt) in aqueous buffer at pH = 7.4 at 37°C was reported elsewhere as 270 min.[24,75] The electronic spectra of 30 and benzoic acid (27a) in identical aqueous phosphate buffer media have also been reported[75] to be different. The absorbance of 30 was about 75% higher than from **27a** in the λ_{max} region (260-290 nm). Therefore, examination of the UV spectra for a solution of **1a** in aqueous phosphate buffer might show an absorbance corresponding to the intermediate **30**. Absorbance of **30** would be predictably higher[75] as compared with the absorbance for an equivalent amount of **27a**. The exact nature of the spectra would depend upon the relative rates of the steps **1a**→**30** and **30**→**27a**. However, irrespective of the relative rates for the steps **1a**→**30** and **30**→**27a**, the overall rate of the reaction **1a**→**27a** cannot be greater than the rate of the reaction **30**→**27a** if **30** is the only intermediate as envisioned in Scheme I. Consequently, one might observe a decay pattern in the UV spectra similar to that of **30**, for a buffered (with $HPO_4^{=} / H_2PO_4^{-}$) aqueous solution of **1a** with ca. $t_{1/2} \leq 270$ min (half life for **30**) at pH = 7 at 25°C. The UV spectra of an aqueous solution of **1a** in phosphate buffer [$(C)_o = 1.32$ mM] at pH = 7 at 25°C were examined [in the region 250-300 nm covering the λ_{max} for both **27a** and **30**, i.e., 273 nm and 275 nm, respectively] from $t_o + 5$ min to $t_o + 12$ hr at different time intervals. No change occurred in the spectra during the period of 12 hr and the spectra were identical with those taken of authentic solutions of benzoic acid under identical conditions. Moreover, spectra of benzoic acid solutions were not affected by the presence of equimolar quantities of diethyl hydrogenphosphonate (**3**). The above results clearly indicate instantaneous (< 5 min) formation of benzoic acid (**27a**) from **1a** in aqueous phosphate buffer (pH = 7) which does *not* support Scheme I.

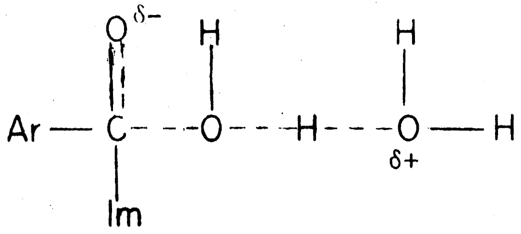
Since Scheme II incorporates the attack of one molecule of water on **1** in the r.d. step, it would seem pertinent to examine the literature regarding attack of water on certain carbonyl compounds which form hydrates and participate in similar reactions. It is generally believed[6,7,8,31] that hydration of reactive ketones or aldehydes involve 2-3 equivalents of water. In one case in the reversible hydration of 1,3-dichloroacetone, the actual order of the reaction has been measured[8] and found to be three with respect to water. The data was validated in solutions containing water in dioxane and water in acetonitrile over a wide range of water concentrations. Formation of an intermediate of the following type was suggested[8] to occur in the r.d. step. In the catalyzed hydration of 1,3-dichloroacetone (catalyzed by benzoic acid or triethylamine), the catalyst molecule could replace one or two molecules of water, respectively, in forming the intermediate.[7,8]



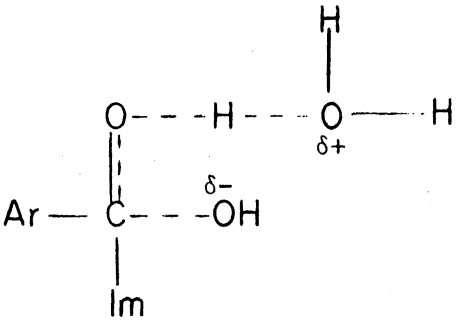
33

R = CH_2Cl

Another reaction which is parallel to the work to be outlined in this thesis is the hydrolysis of (uncatalyzed and imidazole catalyzed) of N-benzoyl imidazole. From a detailed analysis[57] of the kinetics for the above reaction, the observed pseudo first-order rate constants were fitted to a six parameter equation. The following transition states were proposed[57,69] for that phase of the reaction which is independent of the buffer. If the best features of both transition



34a



34b

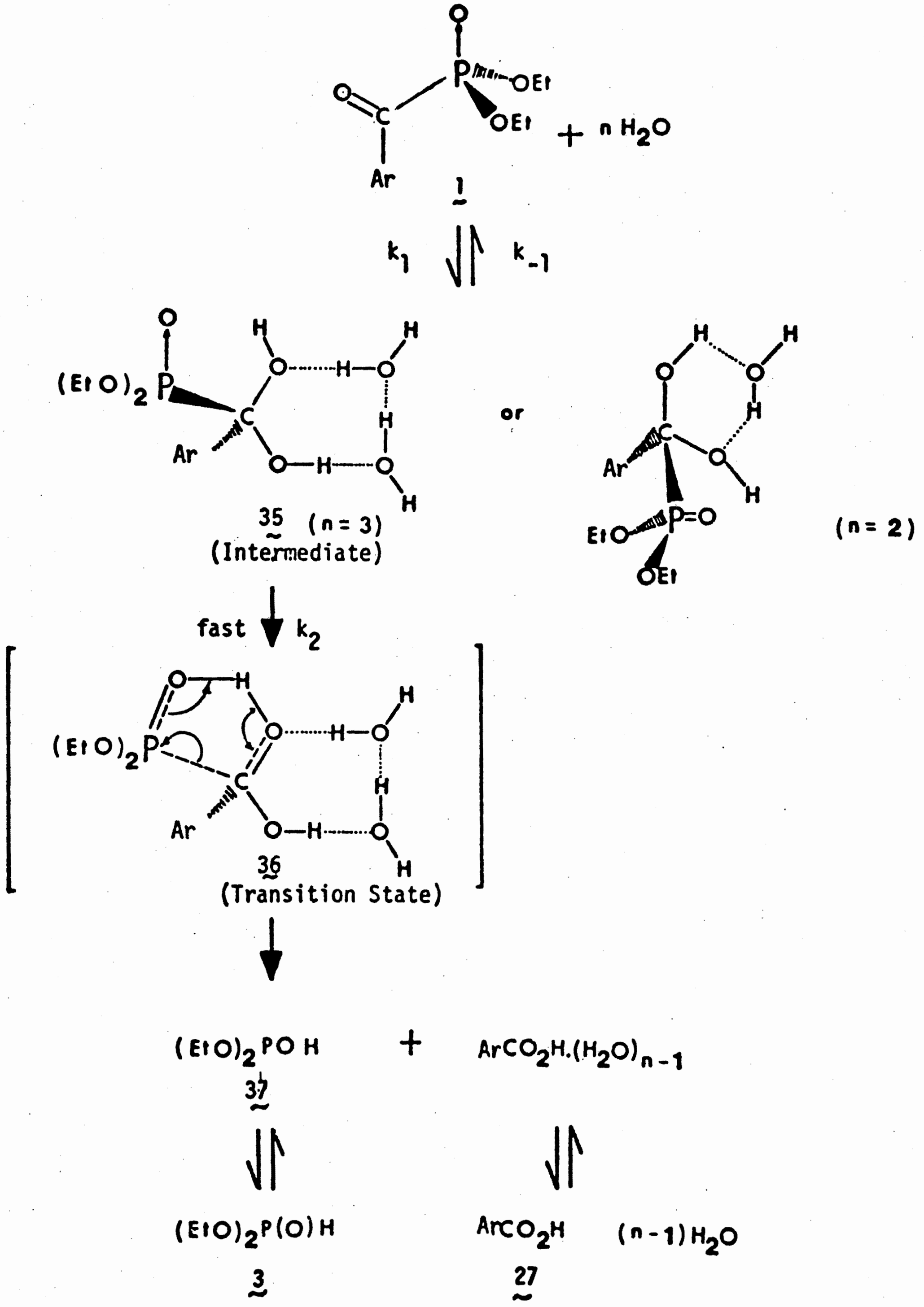
states 34a and 34b are combined, an intermediate in the hydrolysis of 1a (in the absence of buffer) can be envisioned as 35a (Scheme III). Structure 35a is reminiscent of that postulated for the hydration of 1,3-dichloroacetone.[8] Scheme III would be a reasonable pathway for the hydrolysis of 1a in water. As a test for the validity of Scheme III, reaction rates for hydrolysis of 1a would have to be measured in the total absence of any buffer salt.

It is interesting to note that the hydrolysis of acylphosphonates in aqueous sodium hydroxide is infinitely more rapid compared to the reaction in acid.[17,91] However, no kinetic data have been reported. A brief review on various possible methods for a systematic kinetic study for the hydrolysis of 1a in aqueous solution will now be considered.

Since the product of hydrolysis is a carboxylic and, the total acid concentration could be monitored as a function of time to follow the reaction kinetics. However, since the solubility of 1a in water is extremely small (0.2 g per liter at 25°C),[22] conventional acidimetry would not be sensitive enough in aqueous solution of 1a.

As an alternative, an aqueous solution of 1a could possibly be analyzed by GLC as a function of time since analytical procedure for analysis of diethyl hydrogenphosphonate 3 (which would also be another

SCHEME III



(a. Ar = C_6H_5; b. Ar = p-ClC_6H_4; c. Ar = p-MeC_6H_4;)

product of the reaction) has been described.[77] However, techniques of GLC analysis may not be applicable in the case of hydrolysis of 1a → 3 + 27a since side reactions[70,93] could occur on the column at elevated temperature.

Polarographic analysis on solutions of 1a has been reported[16,79] and could be used as an analytical tool for following the kinetics of hydrolysis of 1a. However, polarographic methods of analysis would require the presence of supporting electrolytes and the presence of supporting electrolytes could affect the rate of hydrolysis by acting as a general base.[2,56]

Examination of ^{31}P NMR signals in solution would potentially give very valuable information regarding the nature of the intermediates. The method itself, however, may not be applicable for obtaining accurate rate data for hydrolysis of 1a. The solubility of 1a in water is extremely low but the high natural abundance of ^{31}P would probably permit the spectra to be obtained only in the F.T. mode[34] with pulsing for several hr. Therefore, the signals observed would correspond to the average concentration of the species over the period of pulsing.

Analysis from UV absorbance measurements appears to be the superior method for measuring reaction rates in aqueous solutions of 1a. The data on Table II and III (see also Discussion section) clearly indicate that the $\pi \rightarrow \pi^*$ band for Ia at λ_{max} = 268 nm is sensitive enough (log ε = 3.64) for monitoring the changes in concentrations of the absorbing species in aqueous solutions of 1a. The alternative $n \rightarrow \pi^*$ band is not sensitive enough for the low concentrations (of the order of 1 mM) to be obtainable in aqueous medium.

TABLE II

ULTRAVIOLET ABSORPTION DATA FOR DIETHYL BENZOYLPHOSPHONATE (1a) AND FOR BENZOIC ACID (27a)

		λ_{max} (nm) (Log ε)		Literature[a] λ_{max} (nm) (Log ε)	
Compound	Solvent	n→π*	π→π*	n→π*	π→π*
1a	Hexane	379 (1.91)[b]	258 (4.10)[b]	378 (1.89) 379 (1.92)	257 (4.02) 258 (4.05)
1a	Dioxane	377 (1.95)[b]	261 (4.11)[b]	377 (1.82)	261 (4.33)
1a	1:1 v/v Water-dioxane	367 (1.85)[b]	265 (3.97)[b]	367 (1.85)	265 (3.88)
1a	Water	d	268 (3.64)[c]	-	-
1a	Aqueous HCl (0.53mM)	d	268 (3.74)[c]	-	-
27a	Water	273 (2.93)		273 (2.93)	

[a] See references 50 and 56. [b] Slow decay with time was observed. [c] Values obtained by extrapolation.
[d] Concentration in saturated aqueous solution was so small that the n→π* band was not sensitive enough for an accurate determination of λ and ε.

TABLE III

EXPERIMENTAL VALUES OF MOLAR ABSORPTIVITY (ε) IN AQUEOUS AND HYDROCHLORIC ACID SOLUTIONS OF 1a AND 27a

Solvent	ε (M^{-1} cm^{-1})* for	
	$(\varepsilon_{1a})_{t\to o}$	ε_{27a}^{a}
Water	4350 ± 140	800 ± 20
aq. Hydrochloric acid (0.106 mM)	5230 ± 25	810 ± 10
aq. Hydrochloric acid (0.265 mM)	5425 ± 25	815 ± 10
aq. Hydrochloric acid (0.530 mM)	5530 ± 35	880 ± 50
aq. Hydrochloric acid (0.795 mM)	5500 ± 25	875 ± 10
aq. Hydrochloric acid (1.06 mM)	5410 ± 10	855 ± 5
aq. Hydrochloric acid (5.0 mM)	5350 ± 20	840 ± 10
aq. Hydrochloric acid (10.0 mM)	5355 ± 25	880 ± 10

Temp = 25 ± 0.1°C λ = 268 nm

*M^{-1} cm^{-1} = mol L^{-1} cm^{-1}. [a]Values reported are from the least squares slope computed from the experimental values of concentration (C) and absorbance (A) without including the origin point (0,0) in the computation. The slopes were also determined by including the origin (0,0) in the computation. The deviation in ε_{27a} reported in this Table represents the difference between the evaluated slopes. The average deviation for ε_{27a} evaluated from the experimentally measured absorbance was found to be 4%. This average value has been used for the computation of the error in k_{obs} in a model calculation illustrated on page 181.

The technique of high pressure liquid chromatography (HPLC) coupled with a sensitive detecting device such as fluorescence spectroscopy[38] could possibly be a valuable tool in analyzing the reaction for intermediates and for obtaining rate data. Even if the intermediates were difficulty isolable, detection of its presence would be qualitatively useful.

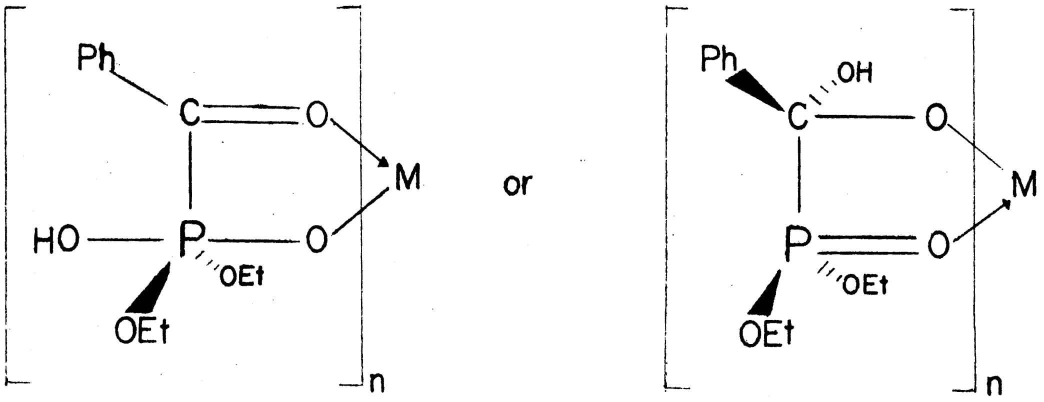
Possible Ramifications of Biological Activity of Ester **1a** in Aqueous Solutions

A general review on phosphates and phosphonates of biochemical interest is available.[52] In preliminary experiments,[94] L-1210 Leukemia ascites tumor cells were treated with compound **1a**, and then injected into C57BL6 mice over a three week immunization period. One week later, the mice were challenged with viable L-1210 cells. The group which had been immunized with the chemically treated cells had an extended survival time of about 2 fold over controls, plus there were two survivors.

The actual experiments were conducted as follows. Interperitoneal fluid was withdrawn from black, male mice (BDF_1 strain) which had been infected with the L-1210 tumor for 7 (seven) days. This fluid contained ascites tumor cells which were filtered and two groups of mice were examined. The ascites cells from one group were treated with a solution of **1a** of concentration $10^{-3}M$ (aqueous ethanol-0.1% ethanol maximum) for 24 hours with stirring. A similar experiment was conducted with a $10^{-4}M$ solution of **1a**. These suspensions of the ascites tumor cells were reinjected back into two new groups of 10 mice each of the same type as cited above. The injections were done twice per week over a three week period (0.1 ml per injection at 3×10^6 cells per ml). A two-week waiting period followed and then a challenge of 10^4 *viable* L-1210 cells (suspensions in phosphate-buffered saline) was injected into the peritoneal cavity. Compared to the control (no injections of tumor cells or of solutions of **1a**), the group of mice with ascites cells previously treated with 10^{-3}M of **1a** lived for 14.5 days while the group which had been treated with 10^{-4}M of **1a** lived 16.7 days (mean survival time compared to a mean survival time of 11.5 days for the control group of mice). The one group which lived 16.7 days had two survivors which lived another 37 days before a new challenge of 5 x 10^7 *viable* ascites tumor cells (suspension as before) were injected at one time. Compared to two other mice which were used as controls (no previous immunization or any type of injections), these two survivors lived another 10 days (the two control mice lived only 5 days).

On the basis of the available information from the literature,[58,87,88,89] various modes of biological action of **1a** in solution are conceivable, such as by direct attack of **1a** on the thiazole (from thiamine) system or imidazole system[58,87,88] present in a biological medium. Biological studies of the half ester-salt, sodium methyl acetylphosphonate, revealed it to be a competetive inhibitor of pyruvate dehydrogenase,[58] for example.

The possibility exists of chelation of metal ions by the action of **1a** in solution and is particularly reasonable in a system such as follows:

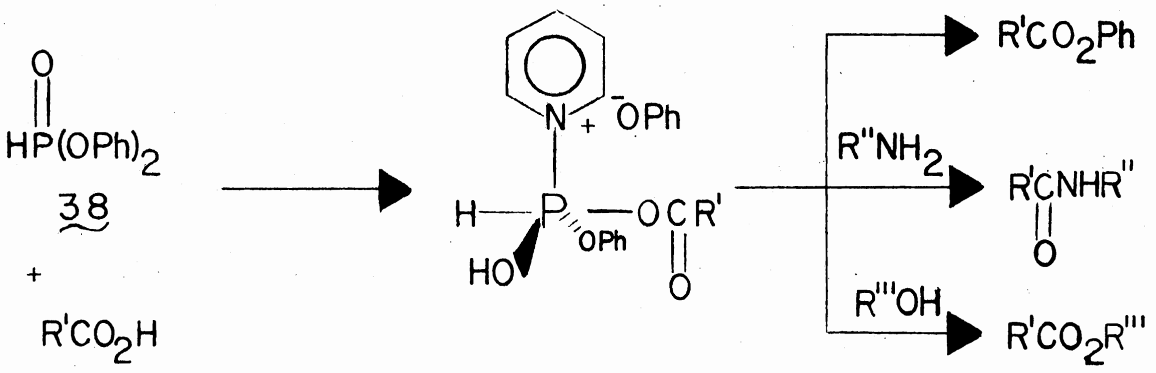


n = 2 or 3

This has *not* been experimentally checked, however. The observation that **1a** almost instantaneously undergoes C-P bond cleavage in aqueous solution in the presence of phosphate buffer at pH = 7 to give benzoic acid (**27a**) and diethyl hydrogenphosphonate (**3**) is suggestive that **1a** may act as a powerful acylation agent *in vivo*.

It has been reported[99] in the literature that diphenyl hydrogenphosphonate (**38**) is a very effective catalyst for the synthesis of polypeptides from the constituent amino acids in presence of pyridine. Under very mild reaction conditions (30-40°C, 0.5-12 hr), synthesis of optically pure esters of amino acids has been reported in good yields (70-80%) with no side reactions.[99] Similar reactions could be initiated by **3** produced from **1a** *in vivo*.

The following mechanism has been proposed for the reaction of **38** by three alternative paths where R' is an amino acid residue. Similar reactions can be envisioned involving **3** although EtO$^-$ is a much inferior leaving group compared to PhO$^-$.


O
HP(OPh)2
38
+
R'CO2H
N+
-OPh
H
P
OPh
HO
O C R'
O
R'CO2Ph
R''NH2
R'CNHR''
O
R'''OH
R'CO2R'''

CHAPTER II

RESULTS AND DISCUSSION

The spontaneous uncatalyzed hydrolysis of 1a in aqueous solution

$$\underset{\text{1a}}{PhC(O)P(O)(OEt)_2} + H_2O \longrightarrow \underset{\text{27a}}{PhCO_2H} + \underset{\text{3}}{HP(O)(OEt)_2}$$

and in presence of externally added hydrochloric acid has been examined by monitoring the $\pi \rightarrow \pi^*$ transition band at $\lambda = 268$ nm, this band being more sensitive than the $n \rightarrow \pi^*$ band[2,56] (Table II, Figure I). Also since 1a was very slightly soluble in water (0.2 g/L),[22] the $n \rightarrow \pi^*$ band could not be used, in our opinion, for monitoring changes in absorbance for such small concentrations (0.2-0.3 mM) employed for reasons stated in the Historical. The effect of UV radiation during the measurement was checked in view of the reported[93] trimerization of 1a and was found to be negligible in aqueous solution in the concentration range studied. Quantitative formation of benzoic acid 27a from 1a was observed at completion of the reaction by UV analysis and using standard solutions of 27a (Figure 2). The other product was identified as diethyl hydrogenphosphonate (3) from ^{31}P NMR spectral analysis (Table IV).

The rates of hydrolysis of 1a in hydrochloric acid (pH 2-4) were measured with a view to screen for any catalytic effect by H_3O^+, if an $A_{AC}1$ or an $A_{AC}2$[53] type of mechanism was operating with the $P(O)(OEt)_2$ moiety as leaving group. Hydrochloric acid solutions were not buffered,

Figure 1. UV Spectra of Diethyl Benzoylphosphonate (**1a**) in Different Solvents.

(---) dioxane

(···) v/v 1:1 water-dioxane

(-·-·) aqueous hydrochloric acid pH $\approx$ 2.04 t_o + 4 hr

(——) water pH $\approx$ 4.5, t_o + 3 min (see Table II).

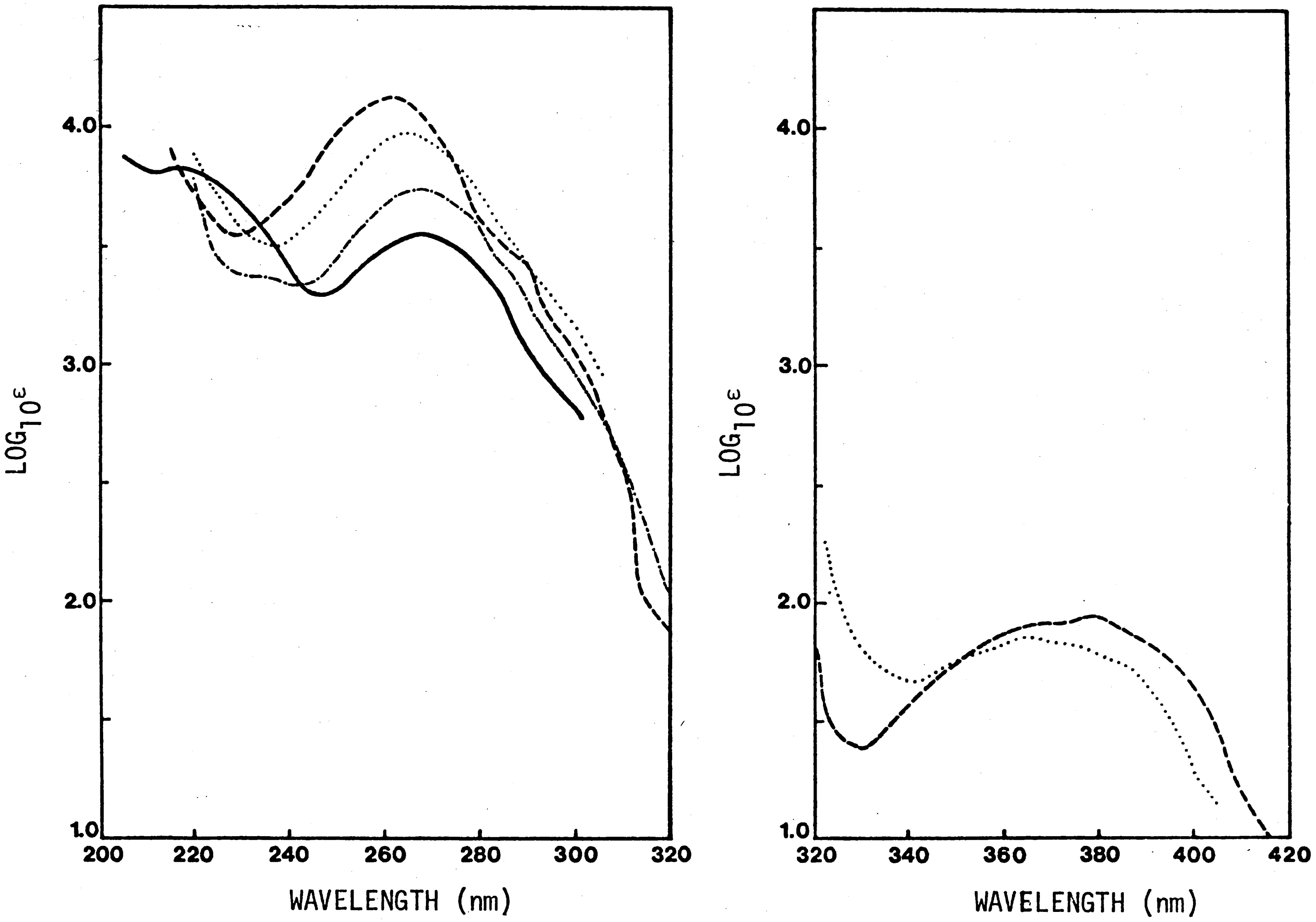

4.0
3.0
2.0
1.0
LOG10ε
200
220
240
260
280
300
320
WAVELENGTH (nm)
4.0
3.0
2.0
1.0
LOG10ε
320
340
360
380
400
420
WAVELENGTH (nm)

Figure 2. UV Spectra of an Aqueous Solution (0.235 mM) of Diethyl Benzoylphosphonate (1a) at Different Time Intervals and an Aqueous Solution (0.237 mM) of Benzoic Acid (27a) at 27°C.

1) *ca.* 0.25 half life
2) *ca.* 0.70 half life
3) *ca.* 1.8 half life
4) *ca.* 10 half life
5) (●) benzoic acid

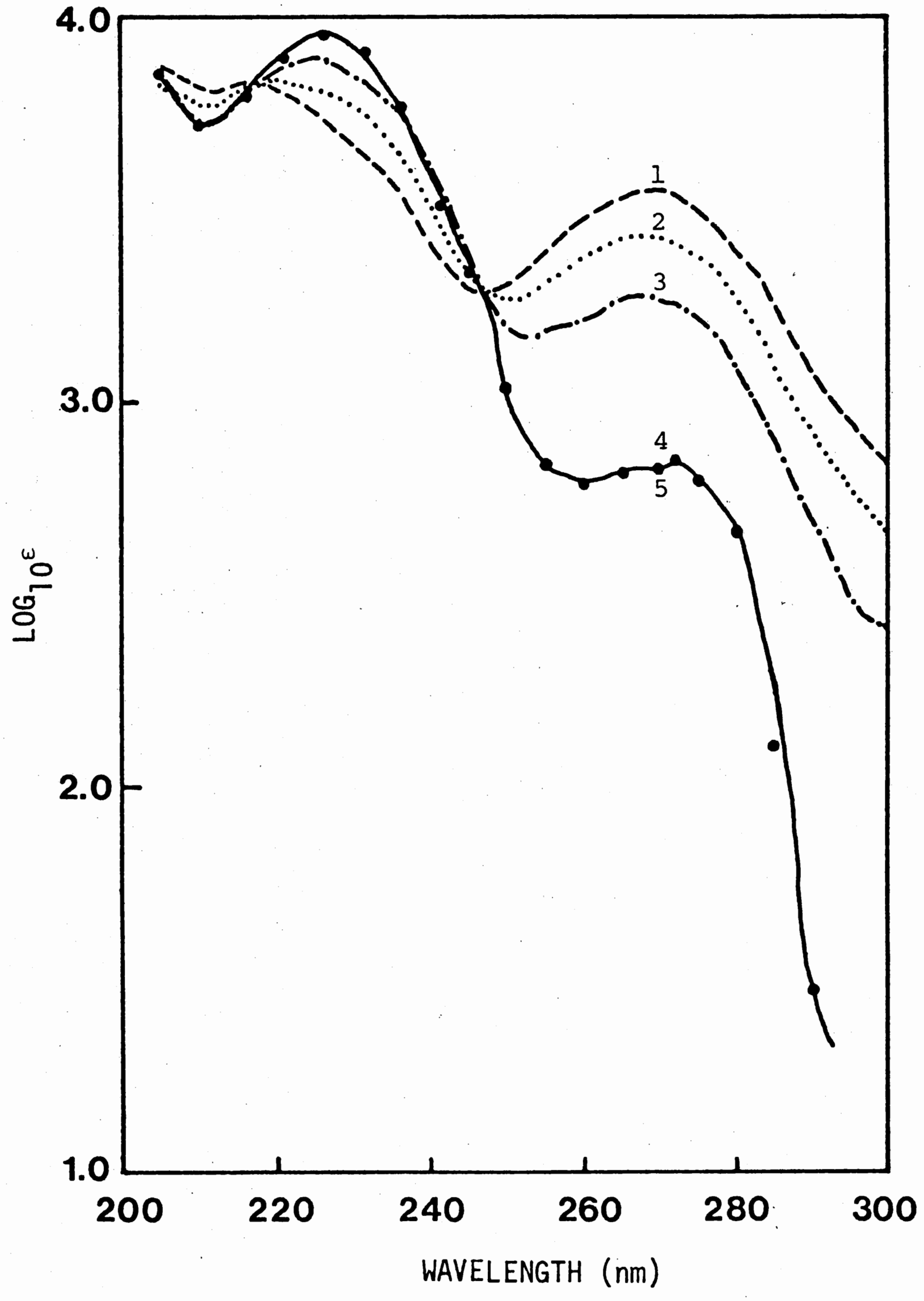

4.0
3.0
2.0
1.0
$LOG_{10}\epsilon$
200
220
240
260
280
300
WAVELENGTH (nm)
1
2
3
4
5

TABLE IV

^{31}P NMR SPECTRAL DATA

Composition	Time (t_o+)			Pulse Parameters^a ACQ	Signals^b (ppm ± 0.1) from 85% H_3PO_4 and $^{I}J_{PH}$ ± 10 Hz		Plate
	Day	Hr	Min				
Solution of 1a in Dioxane, $(C_{1a})_o$ = ca. 0.2 M			5	40	$-1.72^{c,d}$ (1a)		I
Solution of 1a $(C_{1a})_o$ = 0.0235 M C°_{HCl} = 0.9 N^e Solvent^f (v/v 1:1) HCl-Dioxane + D_2O			45	200	-1.2^c (1a)		II(A)
		9 (9.75)	45	200	-1.2^c (1a)	-2.3^g (43a) $+6.5^h$ (680 Hz) (45)	
		16 (16.75)	45	200	-1.2^c (1a)	-2.3^g (43a) $+6.5^h$ (680 Hz) (45)	II(B)

TABLE IV (Continued)

Composition	Time (t_o+)			Pulse Parameters[a] ACQ	Signals[b] (ppm ± 0.1) from 85% H_3PO_4 and $^1J_{PH}$ ± 10 Hz			Plate
	Day	Hr	Min					
Solution of la $(C_{la})_o$=ca. 0.07 M C°_{HCl} = 0.9 N[e] Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O	1	5 (29.0)	-	160	-1.21[c] (la)	-2.3[g] (43a)	-2.9[i] (51a)	II(C)
						+6.5[h] (680 Hz) (45)	+4.0[j,k] (680 Hz) (52)	
					0.0 (weak) (39a)?		+16.3 (weak) (40a)?	
Solution of la $(C_{la})_o$ = 0.0235 M C°_{HCl} = 0.9 N[e] Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O	5	23 (143.25)	15	200	---	-2.3[g] (43a)	-2.9[i] (51a)	III(A)
						+6.5[h] (680 Hz) (45)	+4.0[j,k] (670 Hz) (52)	
							+3.7[l] (100 Hz) (52D)	
	14	23 (359.0)	-	200	---	-2.3[g] (43a)	-2.9[i] (51a)	III(B)
							+4.0[j,k] (670 Hz) (52)	
							+3.7[l] (100 Hz) (52D)	

TABLE IV (Continued)

Composition	Time (t_o +)			Pulse Para-meters[a] ACQ	Signals[b] (ppm ± 0.1) from 85% H_3PO_4 and $^1J_{PH}$ ± 10 Hz			Plate
	Day	Hr	Min					
Solution of 1a $(C_{1a})_o$ = 0.0235 M $C°_{HCl}$ = 0.9 N[e] Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O	59	22 (1439.5)	30	200	---	--- ---	-2.9[i] (51a) +4.0[j,k] (670 Hz) (52) +3.7[l] (100 Hz) (52D)	III(C)
Solution of 3 in D_2O, and Trace of HCl $(C_3)_o$ = ca. 0.2 M	-	-	5	40	+11.25[m,n] (720 Hz) (3)			IV
Solution of 3 $(C_3)_o$ = ca. 0.2 M $C°_{HCl}$ = 0.9 N, Solvent-(v/v 1:1) HCl-Dioxane + D_2O	-	-	5	140	+9.97[m] (710 Hz) (3)	+6.49[h] (680 Hz) (45)		V(A)
	15	- (360.0)	-	80			+4.0[j] (680 Hz) (52) +3.7[l] (100 Hz) (52D)	V(B)

TABLE IV (Continued)

Composition	Time (t_o +)			Pulse Parameters[a] ACQ	Signals[b] (ppm ± 0.1) from 85% H_3PO_4 and $^1J_{PH}$ ± 10 Hz			Plate
	Day	Hr	Min					
Solution of 3 $(C_3)_o$ = ca. 0.45 M C^o_{HCl} = 0.9 N[e], Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O	-	4	-	64	+10.15[m] (710 Hz) (3) +9.32[o] (109 Hz) (3D)	+6.59[h] (680 Hz) (45) +6.32[o] (102 Hz) (45D)	+3.97[j] (670 Hz) (52)	VI(A) VII(A)
Solution of 3 in 1.06 mM Aqueous HCl[p] $(C_3)_o$ = ca. 0.45 M	1	4 (28)	-	64[q]	+11.26[m] (720 Hz) (3)	+6.74[h] (660 Hz) (45)	+4.25[j] (665 Hz) (52)	VI(B)
Solution of 3 $(C_3)_o$ = ca. 0.45 M C^o_{HCl} = 0.9 N[e] Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O Broad ^1H decoupled Spectra	-	4 (4.33)	20	48	+10.15[i] (3) 9.32[o] (109 Hz) (3D)	+6.59[i] (45) 6.32[o] (102 Hz) (45D)	+3.97[i] (52)	VII(B)

TABLE IV (Continued)

Composition	Time (t_o+)			Pulse Parameters[a] ACQ	Signals[b] (ppm ± 0.1) from 85% H_3PO_4 and $^1J_{PH}$ ± 10 Hz	Plate
	Day	Hr	Min			
Solution of 1a $(C_{1a})_o$ = ca. 0.07 M C°_{HCl} = 0.9 N[e] Solvent[f]-(v/v 1:1) HCl-Dioxane + D_2O Broad ^1H decoupled Spectra	1	6 (30)	-	160	-1.34[i] (43) (Predominant) -2.35[i] (51) (Predominant) +10.15[i] (3) (Weak) +6.59[i] (45) +3.97[i] (52) +6.32[l] (102 Hz) (45D) +17.40[i] (40a)? +16.3[i] (40a)? 0.0[i] (39a)?	VII(C)
Suspension of 1a; 17 mg in 3 mL of 1.06 mM Hydrochloric Acid[p]			15	3500[r]	-0.3[c] (39a) (Predominant) +17.9[c] (40a) (Predominant) +11.3[m,s] (720 Hz) (3)	VIII(A)
	1	3 (27.5)	30	3500[t]	-0.3[c] (39a) +17.9[c] (40a) +11.3[m] (720 Hz) (3)	VIII(B)

TABLE IV (Continued)

Composition	Time (t_o+)			Pulse Parameters^{a} ACQ	Signals^{b} (ppm ± 0.1) from 85% H_3PO_4 and $^{I}J_{PH}$ ± 10 Hz			Plate
	Day	Hr	Min					
Suspension of **1a**; 17 mg in 3 mL of 1.06 mM Hydrochloric Acid^{p}	2	4 (52)	-	3500^{u}	-0.3^{c} (**39a**) (Weak) +11.3^{m} (720 Hz) (**3**) (Predominant)	+17.9^{c} (**40a**) (Weak)	6.6^{h} (660 Hz) (**45**) (Weak)	VIII(C)
Suspension of Ester **1a** 17 mg in 3 mLq H_2O^{p}			5	216	+17.9^{c} (**40a**)	-0.3^{c} (**39a**)		IX(A)
Suspension Described in IX A + Large Excess (*ca.* 100 mg) of Ester **1a**			65	36	+17.9^{c} (**40a**)	-0.3^{c} (**39a**)	-1.9^{c} (**1a**) (Predominant)	IX(B)
Suspension Described in IX A + Large Excess (*ca.* 300 mg) of Ester **3**		1 (1.25)	15	36	+17.9^{c} (**40a**) (Weak) +11.3^{i} (720 Hz) (**3**) (Predominant)	-0.3^{c} (**39a**) (Weak)	-1.9^{c} (**1a**)	IX(C)

TABLE IV (Continued)

Composition	Time (t_o+)			Pulse Parameters[a] ACQ	Signals[b] (ppm ± 0.1) from 85% H_3PO_4 and $^{1}J_{PH}$ ± 10 Hz			Plate
	Day	Hr	Min					
Solution of **1b** in Dioxane, $(C_{1b})_o$ = *ca.* 0.2 M			5	64	-1.92^c (**1b**)			X(A)
Suspension of **1b** (*ca.* 17 mg in 3 mL of 1.00 mM Hydrochloric Acid)[p]			5	360	-1.92^c (**1b**)	$+17.56^c$ (**40b**)	-0.65^c (**39b**)	X(B)
			5	3200^v	-1.92^c (**1b**) $+11.35^i$ (720 Hz) (**3**)	+17.56 (**40b**)	-0.65^c (**39b**)	X(C)
Solution of **1c** in Dioxane, $(C_{1c})_o$ = *ca.* 0.3 M			5	20	-1.4^c (**1c**)			XI(A)
Suspension of **1c**; *ca.* 17 mg in 3 mL of 1.0 mM Hydrochloric Acid[p]			5	3200^w	-1.4^c (**1c**) 11.53^i (730 Hz) (**3**) (Weak)	$+18.12^c$ (**40c**)	0.0^c (**39c**)	XI(B)

TABLE IV (Continued)

[a] Pulse parameters used were: Delay time (D5) between pulses = 15 sec and pulse width (P2) = 11.8 μsec. ACQ denotes the number of acquisitions. [b] $\delta > 0$ means downward from 85% H_3PO_4. [c] Quintet. [d] For neat liquid $\delta = -2 \pm 1$ upfield from 85% H_3PO_4, (see ref. 95). [e] Total concentration of acid. [f] Concentration of D_2O added as internal lock was 16%. [g] Triplet (arising from a first order coupling with ^{1}H ($^{3}J_{POCH_2}$) which has a nuclear spin quantum number of ½). [h] Doublet of triplet. [i] Singlet. [j] Doublet. [k] For a solution of (3) in water $\delta = +5.4$ ppm from 85% H_3PO_4 with $^{I}J_{PH} = 683$ Hz (see ref. 68). [l] Triplet (arising from a first order coupling with ^{2}D ($^{I}J_{PD}$) which has a nuclear spin quantum number of 1). [m] Doublet of quintet. [n] Without solvent, 3 has a reported $\delta = 8.0$ with $^{I}J_{PH} = 687$ Hz and there is a known downfield shift in δ and the coupling constant $^{I}J_{PH}$ has also been reported to increase in acidic solvents, (see ref. 68 and 85). [o] Triplet of triplet. [p] Proton external lock was used. [q] Peak area ratio 3:45:52 was 1:1.8:0.06 (65% reaction). [r] Signals at +17.9 ppm (40a) and -0.3 ppm (39a) from 85% H_3PO_4 were symmetrical and the peak area ratio was 1.17; peak area ratio for 3:(39a + 40a) was 1:1.8 (35% reaction). [s] Enhancement of the signal was observed by adding authentic sample 3. [t] Peak area ratio 3:(39a + 40a) was 1:0.22 (82% reaction). [u] Peak area ratio 3:(39a + 40a):45 was 1:0.12:0.06 (90% reaction). [v] Peak area ratio 40b/39b was 1.64 and the area ratio 3:(39b + 40b + 1b) was 1:1.32 (43% reaction). [w] Peak area ratio 40c/39c was 0.31 and the area ratio 3:(39c + 40c + 1c) was 1:8.04 (11% reaction). $^{3}J_{POCH}$ were 8-9 Hz in all the appropriate compounds. See Scheme II for structures. Compounds 3D, 45D, and 52D are the corresponding deuterated analogs of 3, 45 and 52, respectively.

since addition of salt for buffering action could possibly result in a catalytic effect of anion of the added salt.[2,56] In the presence of the added salt, any observed catalytic effect could also be the result of either a general base-catalyzed reaction due to the buffer anion or a specific acid-catalytic effect due to H_3O^+. The two effects would be difficult to differentiate.

Hydrolytic reaction of 1a in water as well as in hydrochloric acid solutions (pH = 2-4) was found to be pseudo first-order in the substrate species. The pseudo first-order rate constants for the hydrolysis of 1a in aqueous and hydrochloric acid medium were evaluated by monitoring the $\pi \rightarrow \pi^*$ band. The optical absorption arising from the stoichiometric amounts of 27a produced from 1a was subtracted from the experimentally measured absorbance(see Eq. 2, page 66). Figure 3 and 4 represent the typical first order plots for the hydrolysis of 1a in water and in hydrochloric acid solutions (up to *ca.* 90% completion). Figure 3 also summarizes the pH variation observed during the course of hydrolysis of 1a in water in the absence of hydrochloric acid. (Please note the difference in the time scale on the abscissa of Figures 3 and 4). Figure 5 indicates the concentration functions vs time plots corresponding to zero, first, second and third order rate equations. The experimental data are taken from one of the typical runs carried out for the hydrolysis of 1a in aqueous hydrochloric acid at pH = 3.13 ± 0.03 and 25°C. It is clear from Figure 5 that only the concentration function (ϕ_1) corresponding to pseudo first-order rate equation is linear with time whereas the concentration functions (ϕ_o, ϕ_2 and ϕ_3) corresponding to pseudo zero, second and third order reaction are *not* linear.

Figure 3. (●) Pseudo First-Order Plot for Hydrolysis of Ester **1a** in H_2O at 25 ± 0.1°C.

$(C_{\mathbf{1a}})_o$ = 0.235 mM

(o) pH as a function of time.

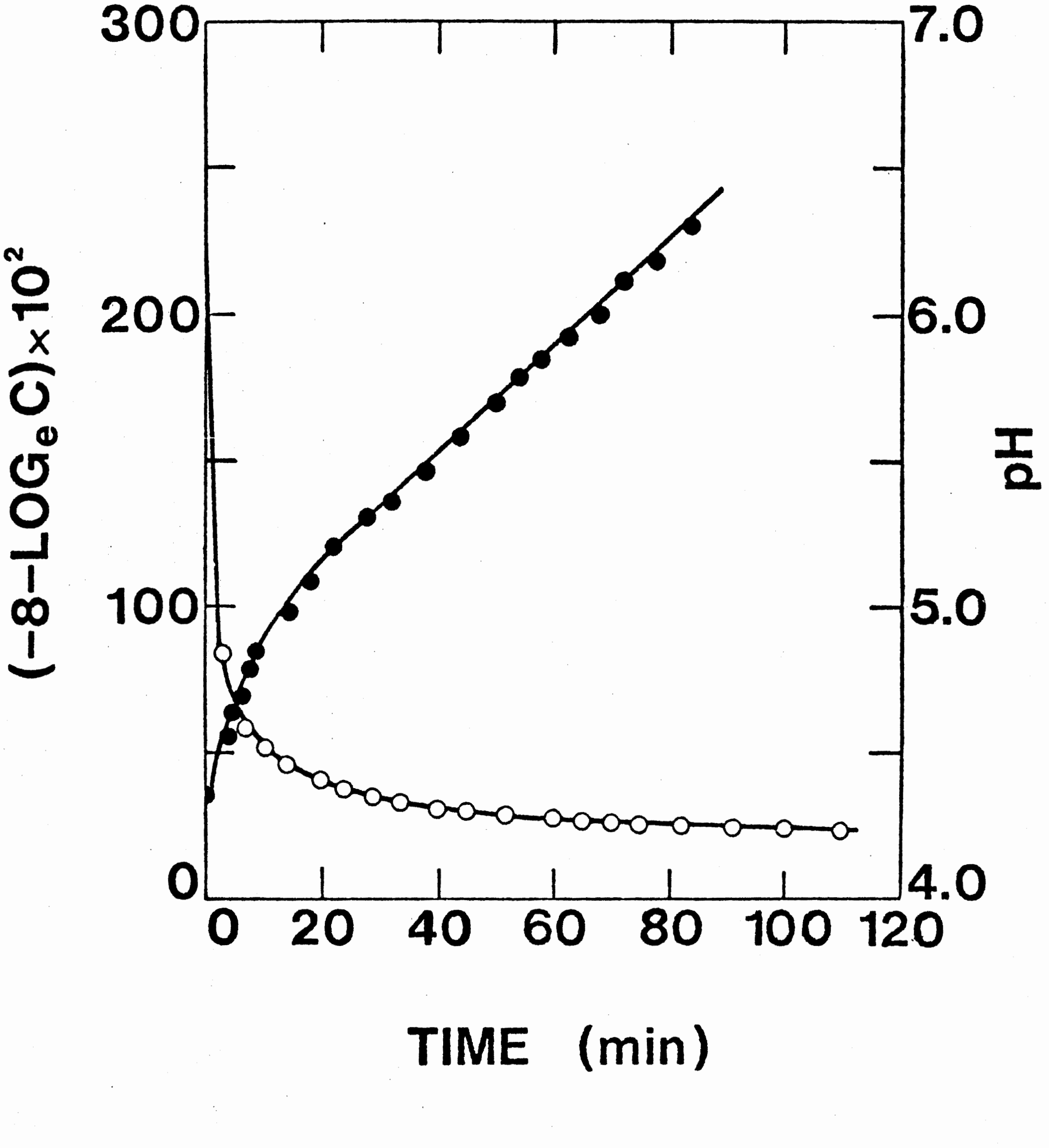

300
200
100
0
7.0
6.0
5.0
4.0
$(-8-\text{LOG}_e\text{C})\times 10^2$
pH
0
20
40
60
80
100
120
TIME (min)

Figure 4. Pseudo First-Order Plot for Hydrolysis of Ester **1a** in HCl at 25 ± 0.1°C.

$(C_{\mathbf{1a}})_o = 0.235$ mM

C_{HCl} (mM): (Δ) 0.106; (◐) 0.265; (●) 0.530; (o) 0.795; (■) 1.060.

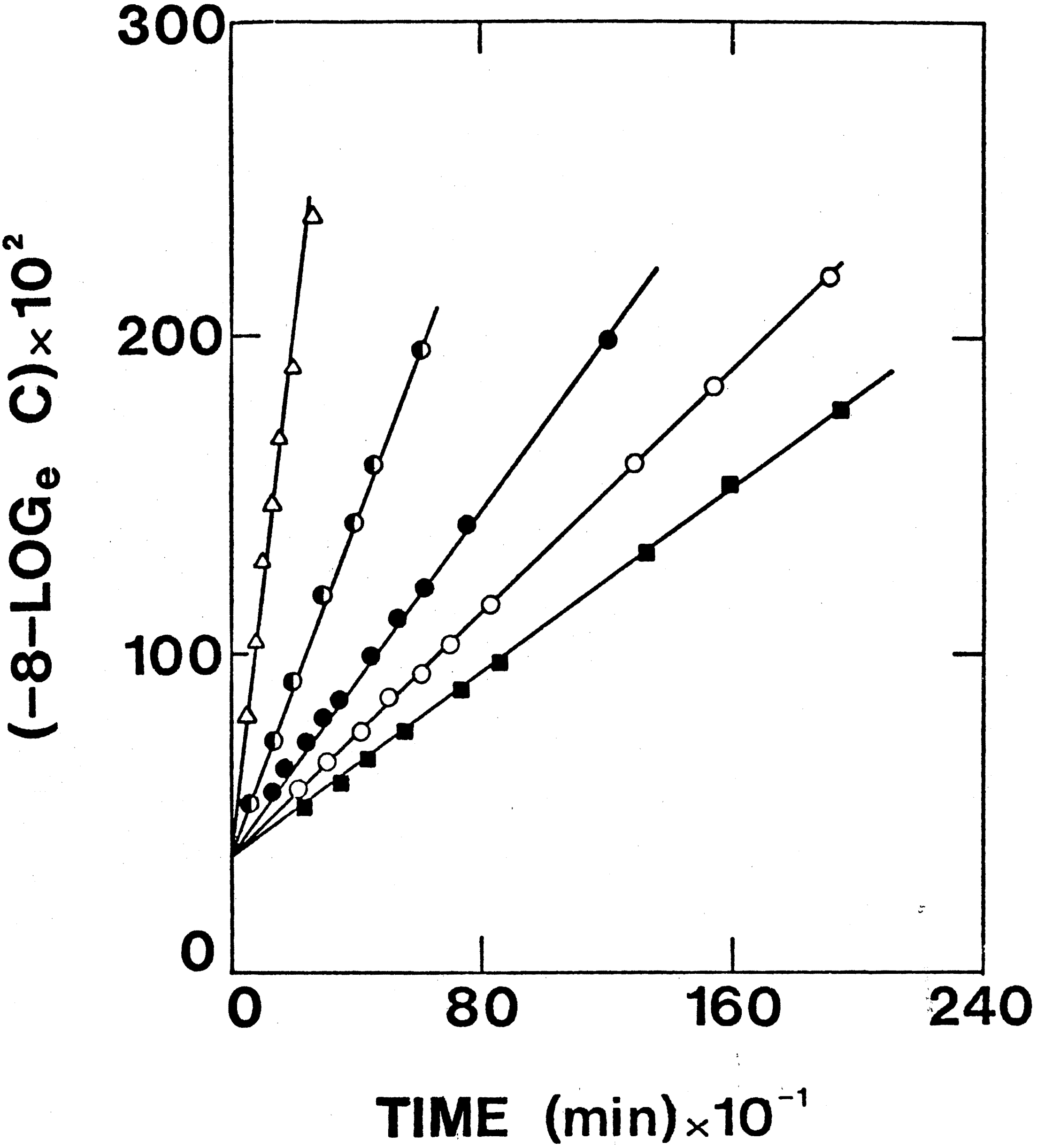

300
200
100
0
(−8−LOG$_e$ C)×10^2
0
80
160
240
TIME (min)×10^{-1}

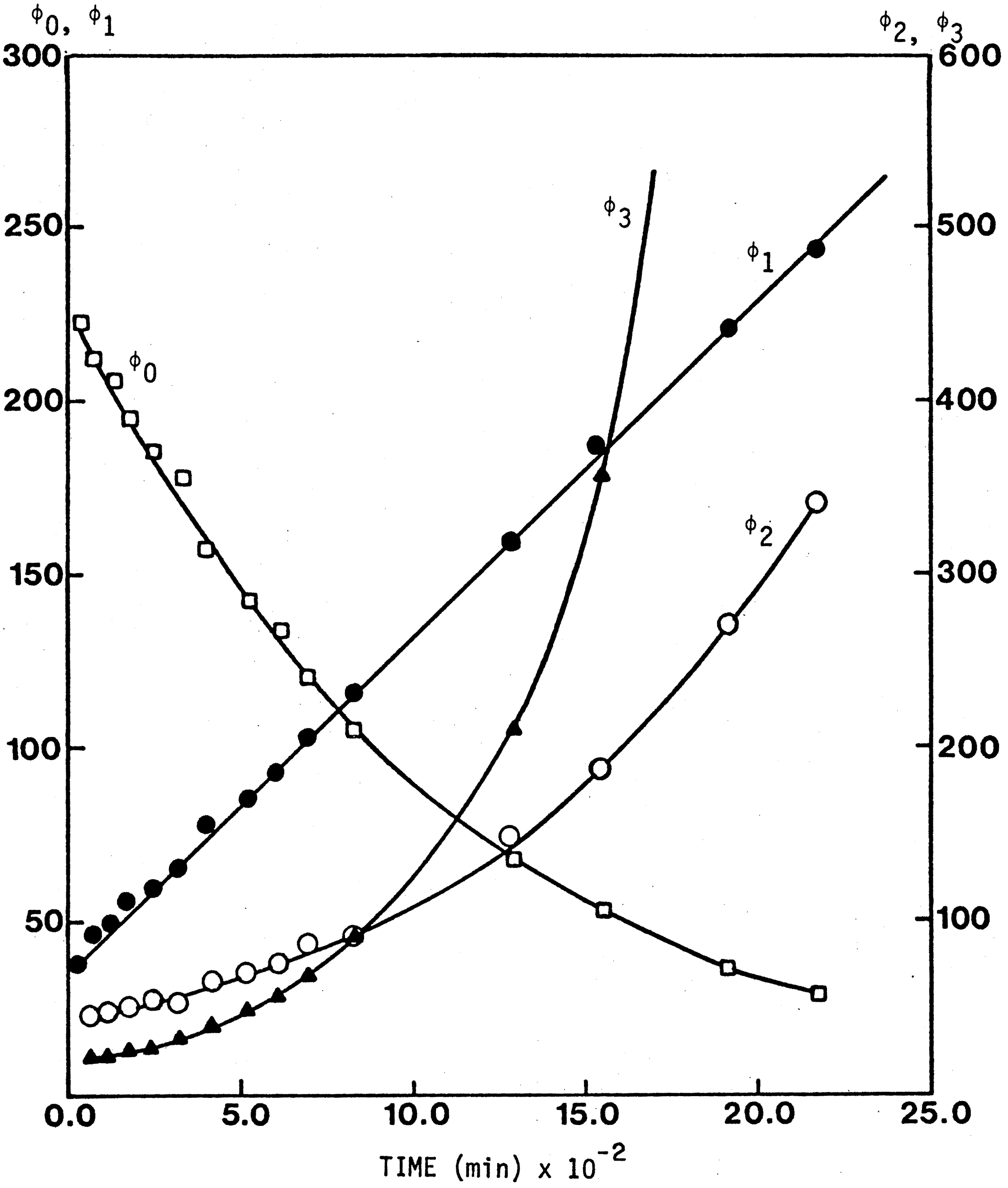
Figure 5. Plot of Concentration Functions versus Time for Zero, First, Second, and Third-Order fit for the Hydrolysis of Ester 1a in Hydrochloric Acid (pH = 3.13 ± 0.03) at 25 ± 0.1°C.

$\phi_0 = (C)_t$ mol $L^{-1} \times 10^6$

$\phi_1 = (-8-\mathrm{Log}_e(C)_t) \times 10^2$

$\phi_2 = 1/(C)_t$ L $\mathrm{mol}^{-1} \times 10^2$

$\phi_3 = 1/(C)_t^2$ $L^2\mathrm{mol}^{-2} \times 10^{-6}$ [from data in Tables XV and XX].


ϕ_0, ϕ_1
ϕ_2, ϕ_3
300
250
200
150
100
50
600
500
400
300
200
100
0.0
5.0
10.0
15.0
20.0
25.0
TIME (min) x 10^{-2}
ϕ_0
ϕ_1
ϕ_2
ϕ_3

Moreover, it is also clear from Figure 4 that the rates of hydrolysis of 1a in acid solutions decreased sharply with increasing concentration of acid [$d\log_{10}k_{obs}/d(pH) = 1.0$ (Figure 6)]. In water in the absence of any external acid, a higher initial rate was observed during the first 15-20% of the reaction (Figure 3) [for a discussion, see page]. This could be due to the initial abrupt fall in pH observed during this period of the reaction, after which a steady state was attained (may be due to self protonation of the reactant). No such higher initial rate was detected in acid solutions (Figure 4) in which pH remained fairly steady (pH ± 0.03). The product of the pseudo first-order rate constant and $C_{H_3O^+}$ was found to be reasonably constant [$(1.2 \pm 0.1) \times 10^{-8}$ mol L^{-1} sec^{-1}] over the range of acid concentrations used (up to pH = 3, see Table V and VI).

^{31}P NMR spectral analysis of solutions of 1a in the presence of a large excess of hydrochloric acid (0.9 N) indicated formation of products arising from cleavage of phosphonyl ester group from both 1a and 3 (Table IV, Scheme IV). This observation imposed a limit of acid concentration (pH = 3) for effecting exclusive C-P bond cleavage without side reactions. In Scheme IV (page 54), intermediates 43a and 51a can also undergo cleavage of C-P bond [like 1a→3] to give the corresponding phosphonic acids 45 and 52. However, these steps would be slower due to the greater possibility of H-bonding in 43a and 51a as compared to 1a. ^{31}P NMR spectral analysis of a suspension (and solution) of 1a in aqueous hydrochloric acid (pH = 3) indicated two distinct signals for intermediates appearing at -0.3 ppm and 17.9 ppm from 85% H_3PO_4 [see Table IV, Plates VIII(A), VIII(B) and VIII(C)]. The above signals have been postulated to arise from a relatively stable pentavalent phosphorus

Figure 6. Log k_{obs} (Pseudo First-Order Rate Constant for the Hydrolysis of Ester 1a in Aqueous HCl) versus pH Plot at 25 ± 0.1°C.

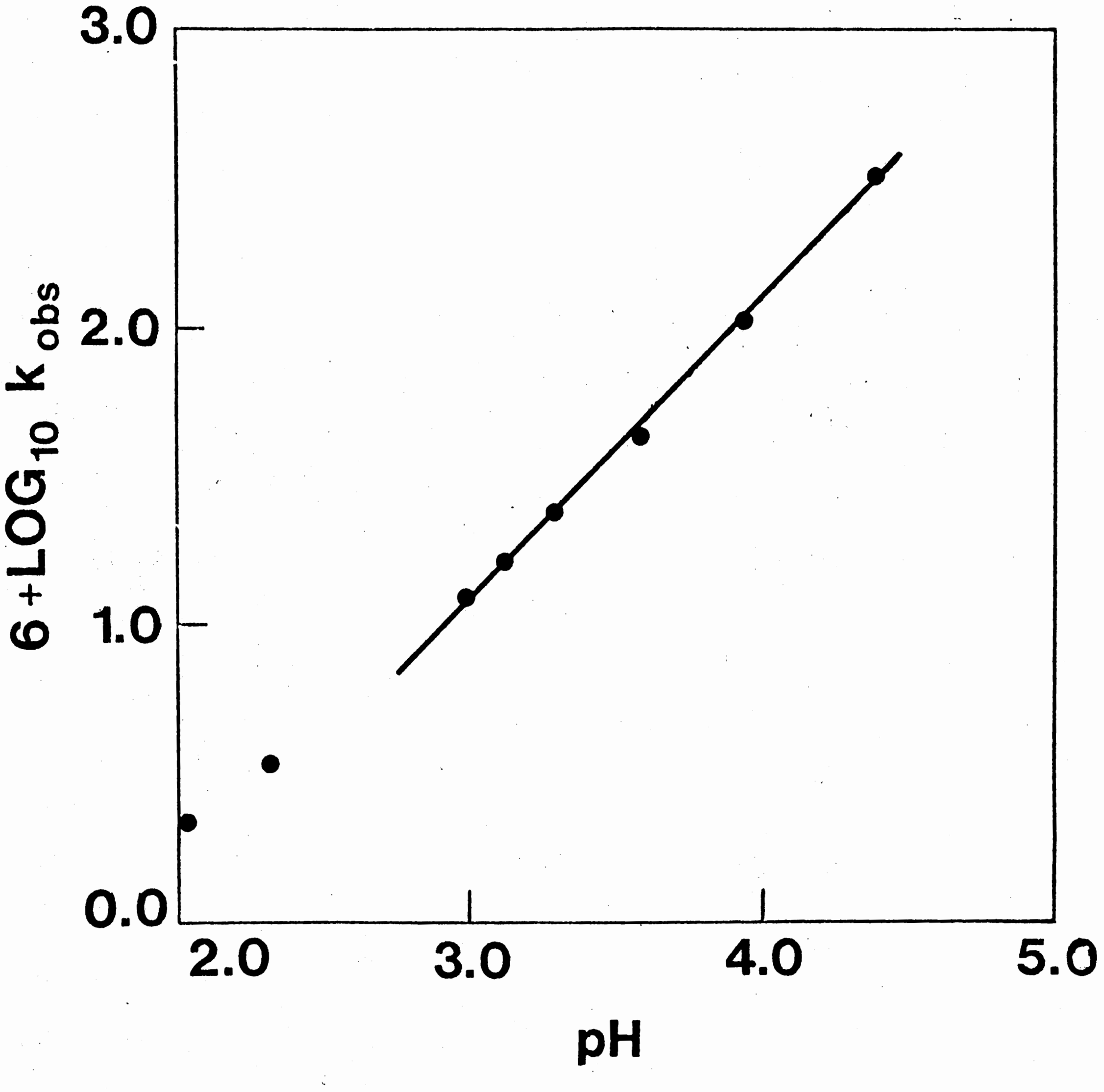

3.0
2.0
1.0
0.0
6 + LOG10 k obs
2.0
3.0
4.0
5.0
pH

TABLE V

PSEUDO FIRST-ORDER RATE CONSTANTS FOR THE HYDROLYSIS OF DIETHYL BENZOYLPHOSPHONATE (1a) IN AQUEOUS AND ACID MEDIA AT TEMPERATURE OF 20-35.5°C AND pH = 2.04-4.40

$(C_{\mathbf{1a}})_o$ mM $\left[(C_{\mathbf{1a}})_o\right]^{a}_{calc}$	C°_{HCl} mM (pH ± 0.03)[b]	Temp T ± 0.1°C	$k_{obs} \times 10^5$ sec^{-1}	R^2[c]	Run
0.235 (0.232)	10.00 (2.04)	30.0 (25.0)	0.380 (0.214)[d]	0.998	1
0.233 (0.230)	5.0 (2.33)	30.0 (25.0)	0.582 (0.333)[d]	0.998	2
0.235 (0.233)	1.06 (3.00)	25.0	1.19	0.999	3
0.233 (0.234)	0.795 (3.13)	25.0	1.57	0.999	4
0.231 (0.231)	0.530 (3.32)	25.0	2.37	0.999	5
0.235 (0.227)	0.265 (3.60)	25.0	4.31	0.999	6
0.235 (0.220)	0.106 (3.94)	25.7 (25.0)	11.6 (10.8)[d]	0.993	7
0.186 (0.178)	0.50 (3.34)	25.0	2.67	0.998	8
0.283 (0.269)	0.50 (3.34)	25.0	2.67	0.999	8
0.246 (0.182)	H_2O[e] (4.4)	25.0	32.4	0.987	9
0.231 (0.187)	D_2O[e] (4.4)	25.0	20.8	0.966	10
0.235 (0.209)	0.265 (3.60)	20.0	2.15	0.999	11

TABLE V (Continued)

$(C_{\underset{\sim}{1a}})_o$ mM $\left[(C_{\underset{\sim}{1a}})_o\right]^{a}_{calc}$	C°_{HCl} mM (pH ± 0.03)^{b}	Temp T ± 0.1°C	$k_{obs} \times 10^{5}$ sec^{-1}	R^{2c}	Run
0.233 (0.218)	0.265 (3.60)	27.5	5.46	0.994	12
0.235 (0.224)	0.265 (3.60)	32.5	9.30	0.999	13
0.239 (0.207)	0.265 (3.60)	35.0	12.26	0.998	14
0.231 (0.191)	H_2O^{e} (4.4)	30.0	44.0	0.986	15
0.231 (0.191)	H_2O^{e} (4.4)	32.5	63.0	0.993	16
0.233 (0.203)	H_2O^{e} (4.4)	35.5	97.0	0.997	17

[a] Values in parentheses indicate those calculated from the least squares line. [b] Values in parentheses are the experimental results. [c] R^2 is the least squares correlation coefficient defined by

$$R^2 = [\Sigma xY - \Sigma x \Sigma Y/n]^2 \;/\; [\Sigma x^2 - (\Sigma x)^2/n]\;[\Sigma Y^2 - (\Sigma Y)^2/n]$$

where $x = t$ and $Y = -\log_e (C)_t$. [d] Value calculated for 25°C from the Arrhenius equation using the experimental data obtained at higher temperature (30°C for runs 1 and 2, and 25.7°C for run 7) and the experimentally evaluated value of $\Delta H^{\ddagger} = 20 \pm 2$ kcal mol^{-1}. [e] No external acid added, the approximate average of the experimental pH = 4.4.

TABLE VI

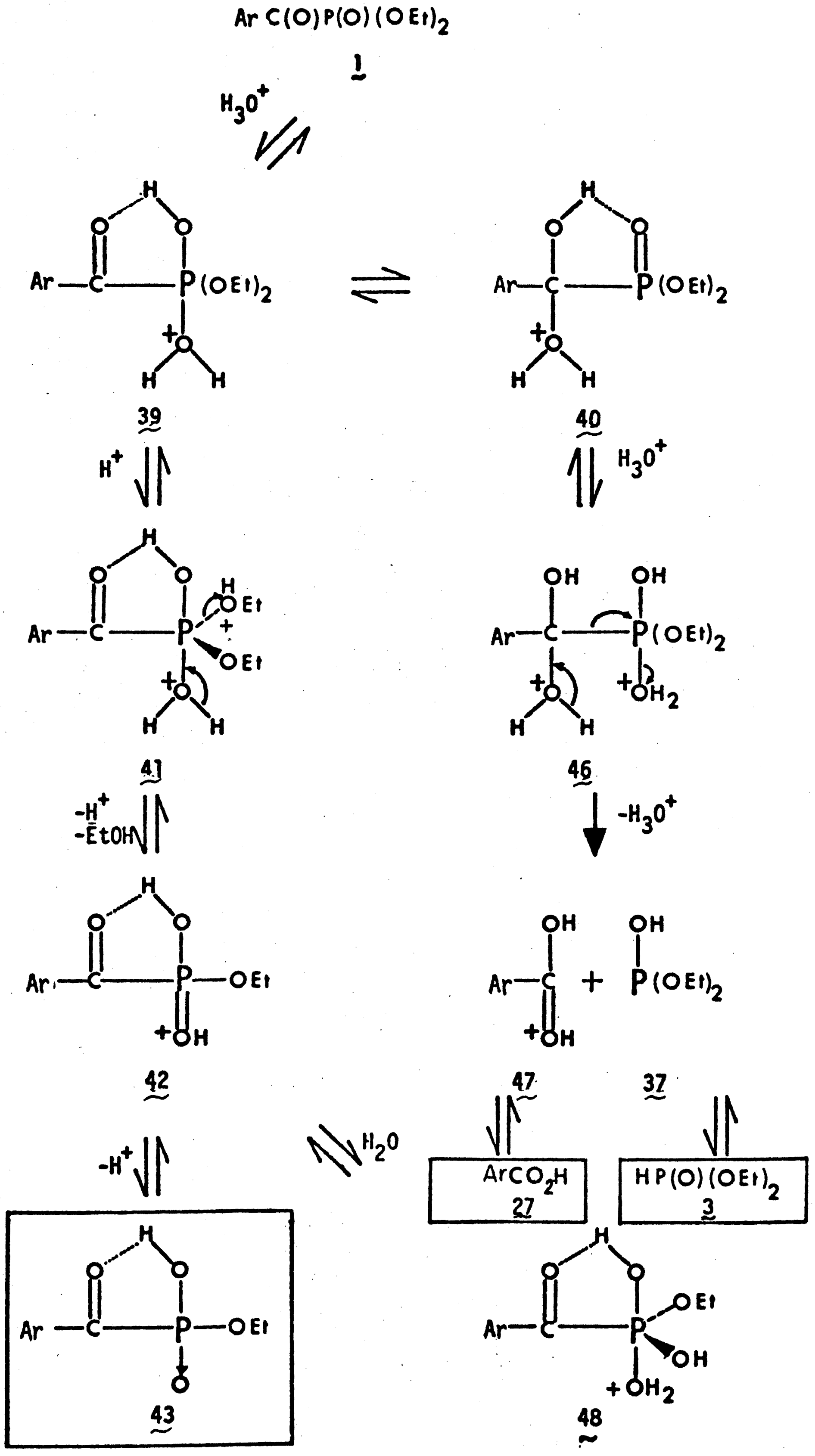
VALUES OF k_{obs} $C_{H_3O^+}$ FOR THE HYDROLYSIS OF ESTER 1a IN AQUEOUS-HYDROCHLORIC ACID SOLUTIONS AT 25°C AND pH = 2.04-4.40

$(pH)_{average}$ ± 0.03	$C_{H_3O^+}$ (mM.)	$k_{obs} \times 10^5$ sec^{-1}	$6 + \text{Log}_{10}\, k_{obs}$	$k_{obs} \times C_{H_3O^+} \times 10^8$ (mol L^{-1} sec^{-1})
2.04	9.120	0.214[a]	0.3304	1.95[b]
2.33	4.677	0.333[a]	0.5224	1.56[b]
3.00	1.000	1.190	1.0755	1.19
3.13	0.7413	1.570	1.1959	1.16
3.32	0.4786	2.370	1.3747	1.13
3.60	0.2512	4.310	1.6345	1.08
3.94	0.1148	10.74	2.0310	1.23
4.40	0.0398	32.10	2.5065	1.28

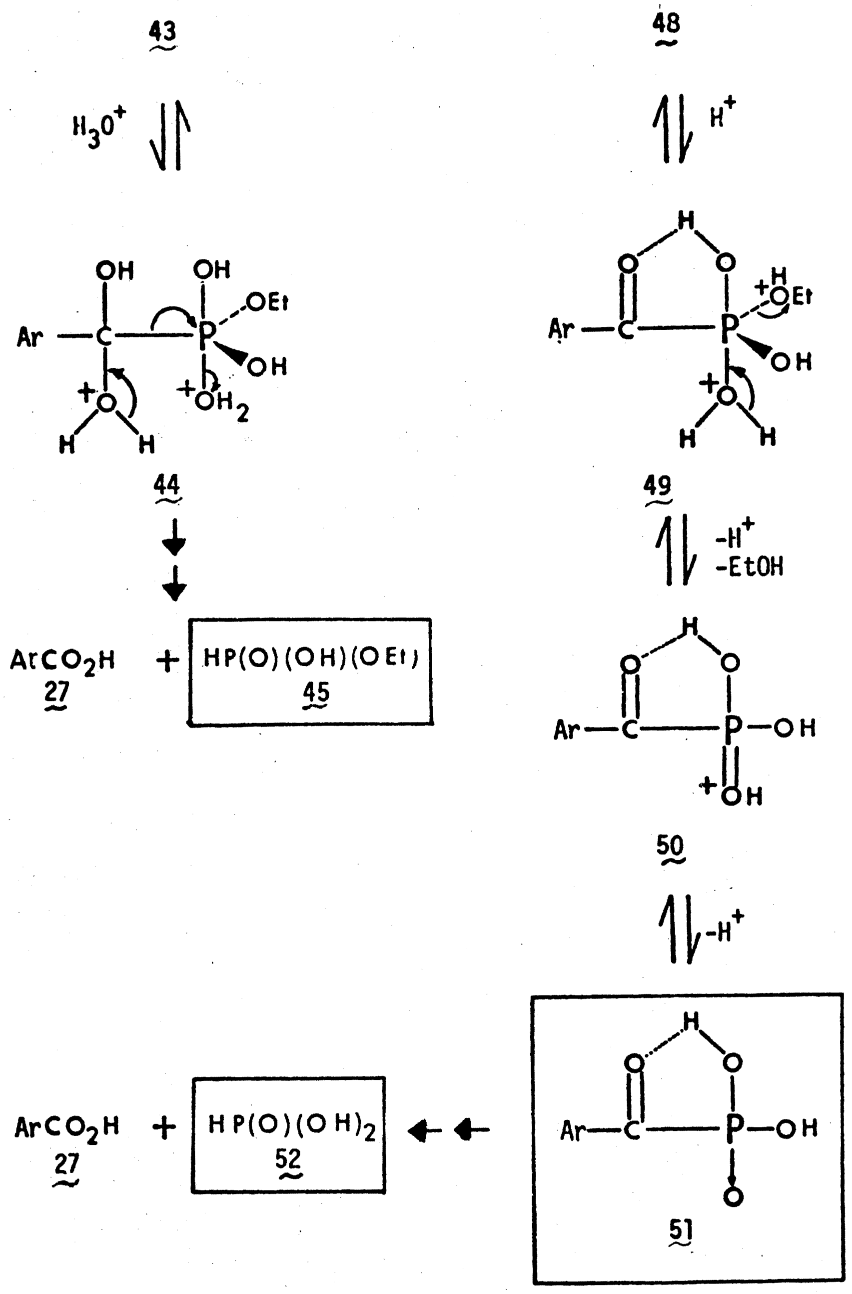
$$k'_{obs} = k_{obs}C_{H_3O^+} = (1.18 \pm 0.07) \times 10^{-8}\text{mol L}^{-1}\text{ sec}^{-1}$$

[a] These are values calculated for 25°C from experimental data at 30°C using $\Delta H^{\ddagger} = 20$ kcal mol^{-1}. [b] These values are much higher and were not included in computing the average (see Discussion). The average value of k'_{obs} calculated from the least square intercept in the Eq.: $\log_{10}k_{obs} = pH + \log_{10}k'_{obs}$ (derived from the Eq.: $k'_{obs} = (k_{obs}C_{H_3O^+})$ was found to be 1.15×10^{-8}mol L^{-1}sec^{-1}; corresponding values of slope and R^2 were: slope = 1.0006; $R^2 = 0.996$. Alternatively $C_{H_3O^+}$ could be computed from C°_{HCl} considering the observed variation in pH as arising from errors in experimental measurements. In such a case $k'_{obs} = k_{obs}C^\circ_{HCl}$ was evaluated as $(1.22 \pm 0.07) \times 10^{-8}$mol L^{-1} sec^{-1}.

SCHEME IV (IN EXCESS ACID)



SCHEME IV (IN EXCESS ACID) (Continued)



(a. Ar = C_6H_5; b. Ar = p-ClC_6H_4; c. Ar = p-MeC_6H_4)

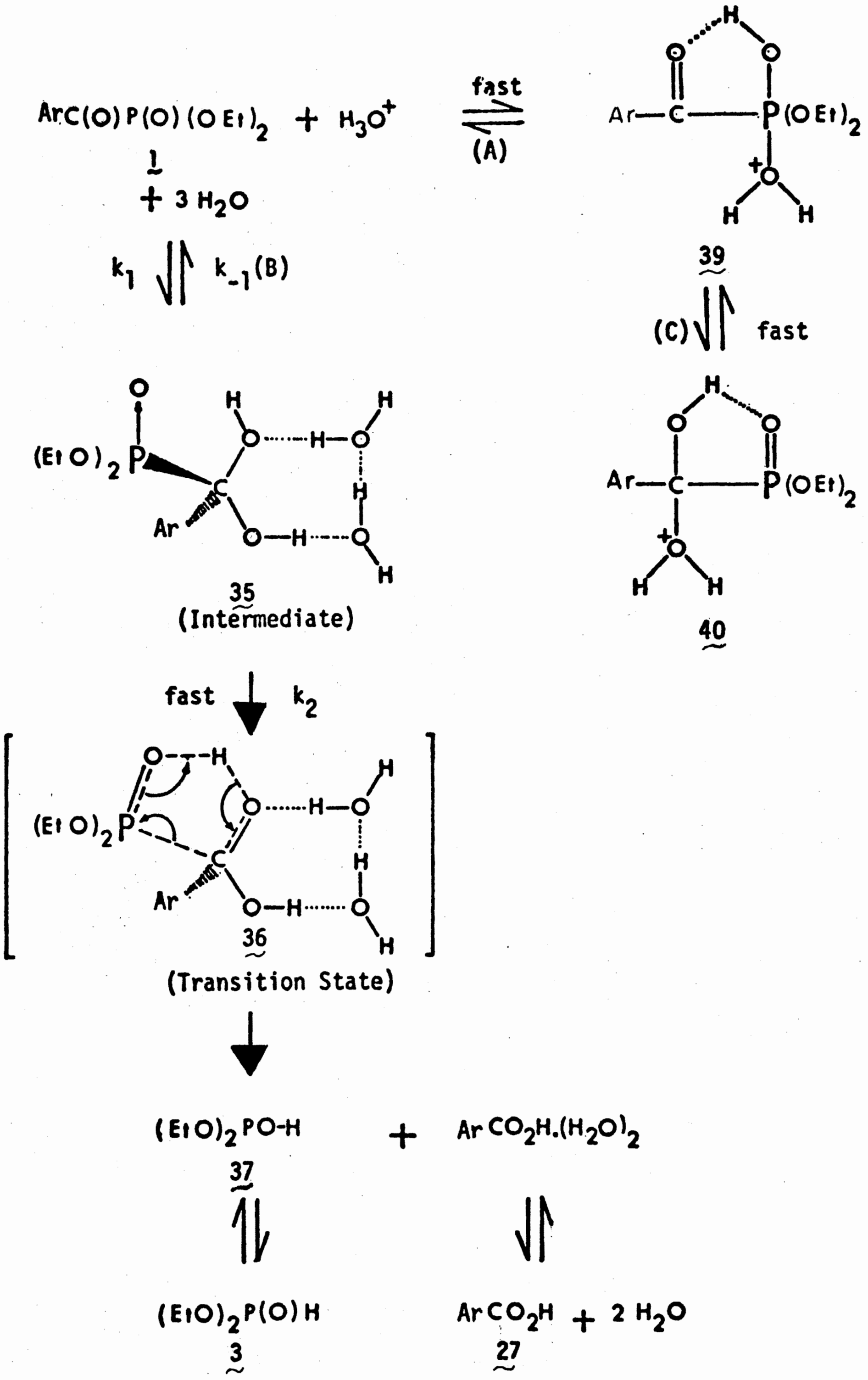
species (phosphonyl hydrated form 39a) and a carbonyl hydrated form 40a (Scheme V) (page 64). Similar signals were also observed in the ^{31}P NMR spectra of suspensions (and solutions) of diethyl p-chlorobenzoylphosphonate (1b) (at -0.6 ppm and 17.5 ppm from 85% H_3PO_4) and diethyl p-toluoylphosphonate (1c) (at 0.0 ppm and 18.1 ppm from 85% H_3PO_4) in 1.0 mM hydrochloric acid after signal accumulation over periods of one to fifteen hr [see Table IV, Plates X(A), X(B), X(C), XI(A), XI(B) and XI(C)]. It is proposed that in the presence of aqueous acid, the protonated, phosphonyl-containing hydrate 39a of ester 1a exists as a part of an equilibrium mixture with 40a. The existence of a mixture of 39a and 40a via an initial fast protonation-hydration of 1a is further supported by Raman spectral and UV spectral data in solution. From Raman spectral analysis of a solution of 1a in D_2O and HCl, the C=O stretching frequency was found to decrease by 4 cm^{-1} although the change was small, it was reproducible (Table VII). The apparent molar absorptivity of 1a was found to decrease considerably (from $\log \varepsilon = 4.10$ to $\log \varepsilon = 3.73$) as the solvent was changed from hexane to aqueous hydrochloric acid ($pH \approx 3$). Moreover, the proposed intermediates 39a and 40a (Scheme IV) also account for the formation of products resulting from cleavage of P-O bonds observed in highly acid solutions via ^{31}P NMR analysis. Mechanisms have been proposed for the hydrolysis of 1a in aqueous and acid solutions. In water, attack of 1a by two (n = 2) or three (n = 3) equivalents of water molecules is predicted to lead to a hydrated intermediate 35a in the rate determining step (Scheme III and V, page 26 and 64). This could reasonably be followed by a fast intramolecular proton abstraction by the phosphonyl oxygen atom. In aqueous acid, a fast protonation of the P=O group is believed to occur initially

TABLE VII

LASER RAMAN SPECTRAL DATA

Sample	Spectra	ν (cm^{-1})
1a Neat	IR	1255 ($P \rightarrow O$) 1662 ($C = O$) 1020 ($P\text{-}O\text{-}C$)
1a Neat	Raman	1260 ($P \rightarrow O$) (broad) 1662 ($C = O$) 1027 ($P\text{-}O\text{-}C$)
$HCl + D_2O$	Raman	1208 - 1550 (broad)
1a in $HCl + D_2O$	Raman	1659 ($C = O$) 1033
1a in D_2O	Raman	1658 ($C = O$) 1036

SCHEME V



(a. Ar = C_6H_5; b. Ar = p-ClC_6H_4; c. Ar = p-MeC_6H_4)

before attack of water. The proposed mechanisms (Scheme V) could account for the experimentally observed rate law, the dependence of the pseudo first-order rate constant on $C_{H_3O^+}$ (in acid), the experimental activation parameters $\Delta H^\ddagger = 20 \pm 2$ kcal mol^{-1}, $\Delta S^\ddagger = -52 \pm 7$ eu (n = 3) and the solvent isotopic effect $k_{H_2O}/k_{D_2O} = 1.6$ as measured in solution. A tentative value for the equilibrium constant for **39a** $\rightleftarrows$ **40a** has been evaluated: $k_{eq} \approx 1.17$ from area ratios of the correspondingly assigned ^{31}P NMR signals.

Identification of Products in Aqueous Solutions

The electronic spectra of the reaction mixture after ten half lives was found to match exactly with the spectra of authentic standard solutions of benzoic acid (**27a**) of nearly identical concentration. This strongly suggests the formation of stoichiometric amounts of **27a** from the spontaneous hydrolysis of **1a** in aqueous solutions (Figure 2). The other product was identified as diethyl hydrogenphosphonate (**3**) from ^{31}P NMR analysis (Table IV) of the reaction mixture. In these experiments, the characteristic ^{31}P NMR signal at +11.3 ppm [from 85% H_3PO_4; $^1J_{PH} = 720$ Hz] for **3** was enhanced by the addition of an authentic sample of **3** (without solvent, **3** has a reported ^{31}P NMR signal at 8.0 ppm with a $^1J_{PH} = 687$ Hz).[29] A downward shift in the ^{31}P chemical shift and a corresponding increase in $^1J_{PH}$ for dimethyl hydrogenphosphonate and also for diethyl hydrogenphosphonate in solvents of varying protonic acidity has been reported.[85] For example, the reported shift difference for the ^{31}P signal for dimethyl hydrogenphosphonate in CCl_4 as compared in F_3CCO_2H is 3.6 ppm and there is an increase in coupling constant as the solvent is changed from CCl_4 ($^1J_{PH} = 691.9$ Hz) to F_3CCO_2H ($^1J_{PH} = 744.3$

Hz). The observations are attributed to the formation of intermolecular hydrogen bonds between the phosphonyl oxygen atom and the hydrogen directly attached to phosphorus in CCl_4[85] as well as to the formation of a 1:1 adduct with the carboxylic acid from solvent through hydrogen bonding at the phosphonyl oxygen atom.

Mathematical Formulation Based on Scheme III

Let the symbols A, C and ε represent the corresponding absorbance, molar concentration and molar absorptivity, respectively. The general equation of hydrolysis can be written as 1a + H_2O → 27a + 3. Let $(C_{1a})_o$ and $(C_{27a})_o$ be the initial concentrations of 1a and 27a, respectively, and $(C_{1a})_t$ and $(C_{27a})_t$ be the corresponding concentrations in the reaction mixture at any instant of time t. From mass balance and stoichiometry it is evident that Eq. (1) assumes that no stable inter-

$$(C_{1a})_t + (C_{27a})_t = (C_{1a})_o \tag{1}$$

mediate builds up in appreciable concentration, and the only species existing in solution in appreciable concentration are the parent ester 1a and products 27a and 3 formed in stoichiometric amounts from 1a. Assuming that the optical absorption in solution due to 1a and 27a is independent of each other, the total absorbance $(A_T)_t$ in solution at any instant of time t (experimentally measured), can be given by Eq. (2), if the only absorbing species at the wavelength used (λ = 268 nm)

$$(A_T)_t = (A_{1a})_t + (A_{27a})_t \tag{2}$$

results from 1a and 27a. From Eqs. (1) and (2), assuming Beer-Lambert law to hold for species 1a and 27a, we can write Eq. (3), the factor ℓ

(path length) is not explicitly included in Eq. (3) since $\ell = 1$ cm in all experiments.

$$(A_T)_t = \varepsilon_{1a}(C_{1a})_t + \varepsilon_{27a}\left((C_{1a})_o - (C_{1a})_t\right) \quad (3)$$

$$(C_{1a})_t = \frac{(A_T)_t - \varepsilon_{27a}(C_{1a})_o}{\varepsilon_{1a} - \varepsilon_{27a}} \quad (4)$$

If Scheme III (see page 26) describes the correct process, the rate of disappearance of 1a would be given by Eq. (5) where C_{35a} is the concentration of the intermediate 35a.

$$-\frac{d\,C_{1a}}{dt} = k_1 C_{1a} C^n_{H_2O} - k_{-1}\,C_{35a} \quad (5)$$

Applying a steady state approximation[11] with respect to 35a (Scheme III), the steady state concentration of 35a could be evaluated from Eq. (6)

$$-\left(\frac{dC_{35a}}{dt}\right)_{ss} = 0 = k_2 C_{35a} + k_{-1} C_{35a} - k_1 C_{1a} C^n_{H_2O} \quad (6)$$

or

$$(C_{35a})_{ss} = \frac{k_1\; C_{1a} C^n_{H_2O}}{(k_2 + k_{-1})} \quad (7)$$

Combining Eqs. (5) and (7) for the steady state, one can get

$$-\left(\frac{d\,C_{1a}}{dt}\right)_{ss} = k_1\; C_{1a}\; C^n_{H_2O} - \frac{k_1\; k_{-1}\; C_{1a}\; C^n_{H_2O}}{(k_2 + k_{-1})} \quad (8)$$

or

$$- \left(\frac{d\, C_{\underset{\sim}{1a}}}{dt} \right)_{ss} = \frac{k_1\, k_2}{(k_{-1} + k_2)}\, C_{\underset{\sim}{1a}}\, C^n_{H_2O} \qquad (9)$$

Equation (9) would predict a pseudo first-order behavior with respect to $\underset{\sim}{1a}$. The integrated form of Eq. (9) is given by Eq. (10).

$$- \log_e (C_{\underset{\sim}{1a}})_t = \frac{k_1\, k_2}{k_{-1} + k_2}\, C^n_{H_2O}\, t - \log_e (C_{\underset{\sim}{1a}})_o \qquad (10)$$

The pseudo first-order rate constant could be calculated from Equation (10) if $(C_{\underset{\sim}{1a}})_t$ is known as a function of t. Equation (4) would give values of $(C_{\underset{\sim}{1a}})_t$ from experimentally measureable absorbance $(A_T)_t$, ε_1, and ε_2, where $\varepsilon_1 \equiv \varepsilon_{\underset{\sim}{1a}}$ or it's equivalent in aqueous solutions and $\varepsilon_2 \equiv \varepsilon_{\underset{\sim}{27a}}$. Values of ε_2 were evaluated at different pH values from absorbance measurements on authentic standard solutions of $\underset{\sim}{27a}$. This has been described under the Experimental section (page 105). Values of ε_1 were evaluated by extrapolative procedure described under the Experimental section (page 106). Thus the pseudo first-order rate constants were obtained for the hydrolysis of $\underset{\sim}{1a}$ in aqueous solutions and in presence of externally added hydrochloric acid by measuring the absorbance from appropriate solutions of $\underset{\sim}{1a}$ as a function of time. The details of the procedure has been described in the Experimental section. The results are summarized in Table V. Equations (4) and (9) could be modified for a situation shown in Scheme V (page 64) in the light of additional evidence for the existence of stable species $\underset{\sim}{39a}$ and $\underset{\sim}{40a}$ produced from $\underset{\sim}{1a}$ by a fast equilibrium step (discussion to follow, see page 91).

Analysis of Kinetic Results and Spectral Data

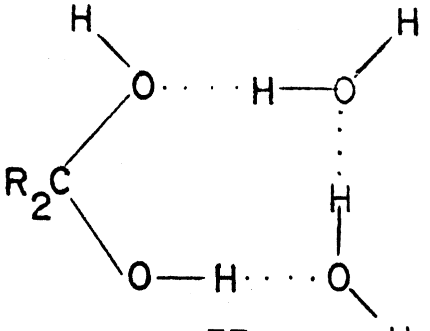
Table V summarizes the data on rate constants for the hydrolysis of 1a in aqueous hydrochloric acid and in water. It is clear from data in Tables V and VI and from Figure 6 that the reaction is definitely retarded as the pH of the medium is lowered. Thus, the reaction becomes slower in more concentrated acid solutions. This is contrary to the expectation if an $A_{AC}1$ or $A_{AC}2$ type of mechanism were operative. The product of the pseudo first-order rate constant and $C_{H_3O^+}$ was found to be $(1.2 \pm 0.1) \times 10^{-8}$ mol L^{-1} sec^{-1} over the range of acid concentrations used in the pH range 3.0-4.4. In strong hydrochloric acid solutions (5.0 mM - pH = 2.33, and 10.0 mM - pH = 2.04), the product of the observed pseudo first-order rate constant k_{obs} and $C_{H_3O^+}$ was found to be much higher (35% and 75%, respectively) in the above solutions than the expected value of 1.2×10^{-8} sec^{-1} mol L^{-1}. The higher values of k_{obs} in the above acid solutions (Table V, Figure 6) could be attributed to simultaneous dealkylation (hydrolysis) of the phosphonyl ester group in 1a and 3 produced from 1a. From the analysis of ^{31}P NMR spectral data on a solution of 1a in 1.06 mM hydrochloric acid at pH = 3.0, ca. 5% dealkylation of 3 produced from 1a was observed to have occurred only after at least four half lives (of 1a). No signal resulting from the phosphonyl ester cleavage of 1a was noticed at pH = 3. However, in highly acidic solutions or from concentrated solutions of 3, acid-catalyzed hydrolysis of phosphonyl ester group from 3 has been reported in the literature[9,10] and there is a known rate enhancement for the acid hydrolysis of 3 as the acid concentration increases.[9,10] In very highly acidic solutions (0.9 N hydrochloric acid + dioxane) of 1a, ^{31}P NMR signals of products formed from phosphonyl ester cleavage were observed (Table IV, Plates I, II and III). In order to account for the pH dependence on the rate constant k_{obs}, Scheme III (see page 26) could be modified, in which one of the water molecules could be replaced by ^{-}OH ions in the formation of an intermediate similar to **35** in the r.d. step. Introduction of this base (in the r.d. step) would result in a general equation for k_{obs} given by Eq. (11).[46]

$$k_{obs} = k_{o} + k_{^{-}OH}C_{^{-}OH} + k_{B}C_{B} \qquad (11)$$

(k_{o} = rate constant for reaction in H_2O)

The constancy of the product of the pseudo first-order rate constant and $C_{H_3O^+}$ observed in solutions up to pH = 3.0 cannot be reasonably explained, in our opinion, by a general base-catalyzed mechanism involving ^{-}OH as the general base in a rate-determining step at pH ~ 3.0. Since the concentration of ^{-}OH is calculated to be of the order of 10^{-11} M in such solutions, no significant contribution from this anion on the rate is likely, unless $K_{^{-}OH} >> k_{o}$ in equation (11). Assuming that a low concentration of ^{-}OH as the only base that could exist in the acid solutions ($k_{B}C_{B} = 0$), calculated values of k'_{o} and $k_{^{-}OH}$ from our experimental results (from a least squares analysis using data from Table VI) were: $k'_{o} = k_{o}/C_{H_2O} = 2.16 \times 10^{-8}$ mol L^{-1} sec^{-1} and $k_{^{-}OH} = 1.1 \times 10^{6}$ mol L^{-1} sec^{-1} at 25°C. Thus, initially one might argue that ^{-}OH could play a vital role in acid hydrolysis. However, such a low value for $k'_{o}/k_{^{-}OH}$ would suggest a negligible catalytic effect due to H_2O from this analysis. Obviously this is unreasonable. An alternative mechanism which could explain the effect of pH on k_{obs} might involve a fast equilibrium prior to the r.d. step (Scheme V, page 64).

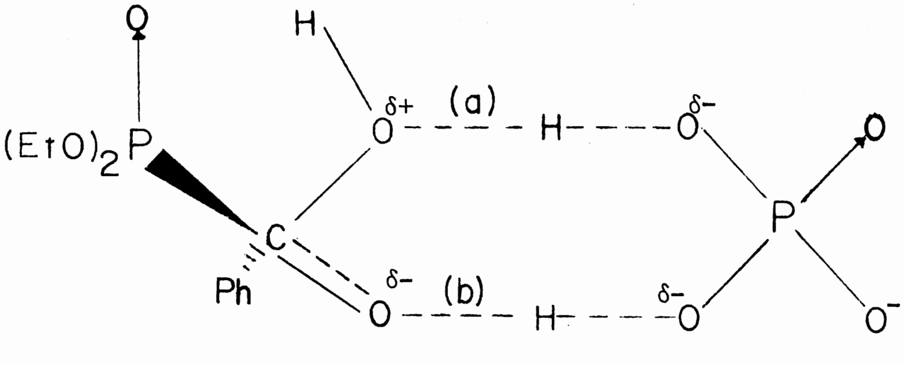
In certain carbon systems, some analogy could be found for our work. For example, Bell and co-workers[6,7,8,31] have shown that three equivalents of water are involved in the r.d. step in the reversible hydration of 1,3-dichloroacetone. Formation of an intermediate 33 was suggested.



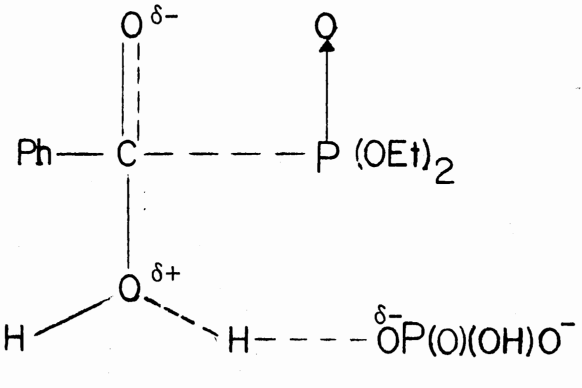
33

R = CH_2Cl

The strong electron-withdrawing chlorine atom on the alpha carbon was important for the formation of a stable hydrate. The reported equilibrium constant at 25°C was 10.0 in favor of the hydrate.[64] Solvent isotopic effects for some of the analogous reactions involving hydration of carbonyl groups can be seen in Table VIII.[7,57,69,80,98] Thus, the low isotopic effect k_{H_2O}/k_{D_2O} = 1.5 reported[2] for the phosphate-catalyzed hydrolysis of 1a in water-dioxane mixture might be explained more accurately by a modified structure for the transition state formed in the r.d. step, as shown in structure 53a, page 72 (Scheme VI, page 74) in contrast to the structure shown in 31a , page 72 (Scheme II, page 22). The primary effect due to deprotonation at point (a) would be reduced by the apparent inverse effect due to O-H bond formation at point (b). Conceptually, the structure in 53a could give rise to an H-bonded intermediate such as 32a followed by a fast intramolecular proton abstration by the phosphonyl oxygen atom as shown in Scheme VI.



$\underset{\sim}{53a}$



$\underset{\sim}{31a}$

Structures for the Proposed Transition States for the Hydrolysis of Ester ($\underset{\sim}{1a}$) by $HPO_4^{=}$ in Aqueous Solutions, see also Scheme VI, page 74 and Scheme II, page 22.

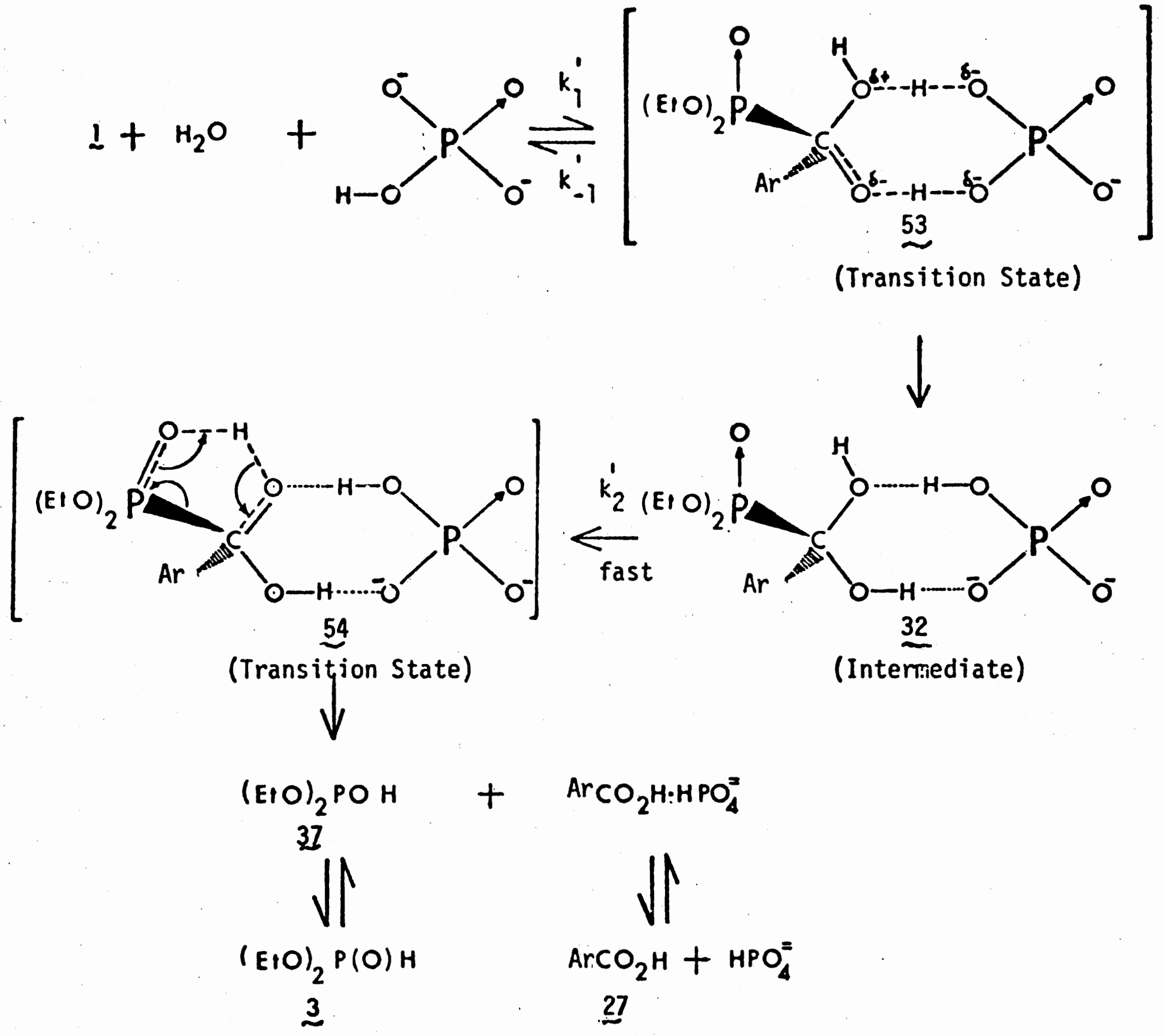
TABLE VIII

SOLVENT ISOTOPIC EFFECT ON RELATED SYSTEMS

Reaction	Medium	Catalyst	k_{H_2O}/k_{D_2O}	Reference
Hydrolysis of **1a**	Dioxane-water v/v (1:4)	$HPO_4^=/DPO_4^=$	1.5^a	2
Hydrolysis of *p*-nitrobenzoyl imidazole	H_2O/D_2O	ImH/ImD	5.57^b (2.01) 0.60^c (0.94)	57,69,80
Mutarotation of glucose	H_2O/D_2O	None	3.8 (3.16)	98
Hydration of 1,3-dichloroacetone	Dioxane H_2O/D_2O	None HCl	3.97 1.23	7

$^a k_{HPO_4^=}/k_{DPO_4^=}$ at pH = 7.0. $^b k_{1(H_2O)}/k_{1(D_2O)}$ and $^c k_{2(H_2O)}/k_{2(D_2O)}$ in the generalized Eq. $k_{L_2O} = k_1 + k_2\ [LO^-]$ where L = H or D. Numbers in parentheses are revised values.

SCHEME VI



(a. Ar = C_6H_5; b. Ar = *p*-ClC_6H_4; c. Ar = *p*-MeC_6H_4)

In aqueous solution in the absence of a catalyst, formation of the intermediate could involve at least two equivalents of water. In comparison with other carbonyl-containing systems **33** (page 71),[7,8] structure **35a** in Scheme III (page 27) would be a reasonable intermediate for the spontaneous hydrolysis of **1a** in *water* in the *absence* of a *catalyst*. In **35a**, free rotation of the C-P bond could occur followed by fast abstraction of a proton in an intramolecular fashion as shown (via the P(O) group in **36a** in Scheme III). This process may logically involve electron shifts resulting in C-P bond cleavage in a concerted step. Such a process of proton abstraction would be more probable, since the rate of C-P bond rotation would be much higher than the rate of collision between **35a** and $^{-}$OH ions in such solutions of low concentration. The product diethyl hydrogen phosphite could quickly equilibrate to the stable phosphonate form.[23,32] Similarly, the other product would be solvated benzoic acid (hydrogen bonded with water molecules) which would be in equilibrium with free benzoic acid and water.[7] Furthermore, the benzoic acid and diethyl hydrogenphosphonate could also exist as a 1:1 adduct.[85] In our work, the gross solvent isotopic effect for the hydrolysis of **1a** carried out in H_2O and D_2O was experimentally measured and k_{H_2O}/k_{D_2O} was found to be 1.6 at 25°C. The low isotopic effect is expected for a transition state involving strong hydrogen bonding between participants and is a situation in which the zero point energy could be conserved.[6,21] It is of interest to note that possible existence of open dimers and trimers in water has been indicated by CNDO/2 calculations.[76] Calculations performed on several different fixed geometric models showed minimization of energy for the dimers and trimers of the order of 7.0-9.5 kcal mol^{-1} compared to the monomer.[76]

Consequently involvement of two molecules of water in the uncatalyzed reaction (or one molecule of water and one equivalent of base in the base-catalyzed reaction) to form a cyclic intermediate such as in 35a in the r.d. step (Scheme III) may not require very high activation energy. The $\Delta H^{\ddagger}$ for the overall reaction was evaluated as 20 ± 2 kcal mol^{-1}.

In aqueous solution in the absence of a catalyst, formation of an intermediate involving only one equivalent of water followed by a fast intramolecular proton abstraction by the phosphonyl oxygen (as in Scheme III, V, or VI - see pages 26, 60 and 64 for these Schemes) could not be ruled out. However, such a process is not likely, since it would be difficult to explain the observation of a general base-catalyzed process reported elsewhere for this reaction.[2]

If a general base-catalyzed mechanism is assumed operative with no participation of the P=O group in acid solution, much experimental data is difficult to defend. For example, ester 1a has a high dipole moment (2.76 D)[65,67] and would be expected to be protonated at P=0 [$-\!\!\!\rangle P{=}O \longrightarrow -\!\!\!\rangle\overset{+}{P}{-}OH$] in aqueous solutions. ^{31}P NMR spectral analysis of a solution of 1a in dioxane-hydrochloric acid solution (0.9 N in HCl, containing 16% D_2O for locking) gave signals corresponding to products 43a [triplet -2.3 ppm ($^3J_{POCH}$ = 9 Hz)] and 51a (singlet -2.9 ppm). These signals were produced from 1a and, in addition, ^{31}P signals appeared corresponding to 45 [doublet of triplets + 6.5 ppm ($^1J_{PH}$ = 680 Hz)], 52 [doublet +4.0 ppm ($^1J_{PH}$ = 670 Hz)] and 52D [the deuterium analog of 52 triplet +3.7 ppm ($^1J_{PD}$ = 100 Hz)].[36] An authentic sample of 3 gave identical signals due to 45, 52 and 52D and also weak signals due to the deuterium analogs of 3 and 45 [(3D and 45D), see Scheme IV, page 60].

The positions (chemical shifts) and multiplicities of the ^{31}P signals were confirmed by observing the ^{31}P spectra in solutions after broad ^{1}H decoupling. (See Table IV and Plates I, II, III, IV, V, VI, and VII). Formation of the above species in solution strongly suggested *direct participation of the P=0 group in acid solutions*.

Raman spectra of **1a** in the liquid state, in D_2O, and in a D_2O-hydrochloric acid suspension were recorded. The C=0 stretching frequency was observed at 1662 cm^{-1} for a neat sample of **1a** which corresponds to the value observed in the IR spectrum. A reproducible shift of 4 cm^{-1} towards smaller wave number was observed for the C=0 stretching frequency in both D_2O and the D_2O-HCl suspensions of **1a** as compared with the value for **1a** neat (Table VII). This was suggestive of structural modification such as involving H-bonding of the C=0 group of **1a** in aqueous and acid solutions. Unfortunately, the P=0 stretching frequency could not be observed, since this region (1255 cm^{-1}) was masked by the broad absorption due to D_2O in the Raman spectrum.

Definite participation of the P=0 group in phosphonates in forming hydrogen bonds in protic solvents and in association with carboxylic acids has been demonstrated in related systems via ^{31}P NMR studies.[85] Intermediates involving a hydrogen bonded phosphonyl group[20,43,45] have been proposed for acid hydrolysis of certain phosphonated acetals and similar systems. Certain phosphonates, including diethyl hydrogenphosphonate, have also been reported[9,10,20,37,78] to undergo dealkylation in strong acid solutions at room temperature following an initial protonation of the P=0 group. Interestingly, from ^{31}P NMR work on dialkyl hydrogenphosphonates in fluorosulfuric acid at -60°C, Olah and co-workers[68] observed large deshielding effects on phosphorus upon protonation. It was concluded that in the protonated phosphonium species the positive charge was largely shifted from phosphorus to the oxygen atom. Such a situation could occur with 1a in acid and may be the cause of occurrence of a ^{31}P NMR signal at lower field as is postulated for 39a or 40a in Scheme V (page 64).

Under the conditions of our experiment (pH 3-4.4), no phosphonyl ester cleavage of 1a (or of 3 that formed) was observed in aqueous and acid solutions for a period of 4 half lives. However, a moderately concentrated solution of 3 (0.45 M) in 1.06 mM HCl at room temperature gave ^{31}P signals corresponding to 45 and 52 [+6.7 ppm ($^{1}J_{PH}$ = 660 Hz) and +4.2 ppm ($^{1}J_{PH}$ = 665 Hz), respectively] in addition to the parent signal for 3 [+11.3 ppm ($^{1}J_{PH}$ = 720 Hz)] when the mixture was analyzed after 28 hours. From peak area ratios of signals corresponding to 3:45:52, it was estimated that about 65% of the total hydrolysis of the phosphonyl ester groups[9,10] had occurred [Table IV, Plate VI(B)]. Analysis of ^{31}P NMR spectra of 1a in 1.06 mM hydrochloric acid (pH ≈ 3.0) observed after 15 hr of signal accumulation gave the following signals. A doublet of quintets centered at +11.3 ppm ($^{1}J_{PH}$ = 720 Hz) was identified as from 3. Addition of an authentic sample of 3 gave peak enhancement in the spectrum. Two more ^{31}P NMR signals, (quintets at -0.3 ppm and +17.9 ppm) appeared and were apparently due to at least one intermediate [39a, 40a; see Table IV, Plate VIII(A), VIII(B) and VIII(C)]. The ^{31}P NMR spectra were recorded on a suspension of 17 mg of ester 1a in 3 mL of 1.06 mM aqueous hydrochloric acid after 3500 acquisitions (15 hr). The spectra were observed at three different time intervals at t_o + 5 min, t_o + 27.5 hr and t_o + 52 hr + time of acquisition (15 hr). Judging from the relative areas under the signals, the extent of reaction at the above time intervals could be estimated as 35%, 82% and 90%, respectively, on an average basis ^{31}P NMR signals from **45** (+6.6 ppm, $^{1}J_{PH}$ = 660 Hz) could be detected (5% as estimated from peak area ratios) only after four half lives on a suspension of **1a** in 1.06 mM hydrochloric acid after signal accumulation for 15 hr [Plate VIII(C)]. The signals appearing at -0.3 ppm (**39a**) and +17.9 ppm (**40a**) were symmetrical and the relative area ratio for signals corresponding to **40a** and **39a** was found to be 1.17 (at 35% reaction) and 1.21 (at 82% reaction). The two signals attributed to **39a** and **40a** (Plate VIII) could be the intermediates, since they appear as soon as **1a** is dissolved in hydrochloric acid and progressively decay with the corresponding appearance of the product signal for **3**. Since the concentration of ^{31}P species would be extremely small in a completely homogeneous aqueous solutions of **1a** the above experiment was performed starting with a suspension of **1a** in 1.06 mM hydrochloric acid. From such a suspension, the concentration of a ^{31}P species would be replenished in the solution as **1a** reacted. The solution was found to be clear at the end of the experiment.

Spectra were also recorded in a completely homogeneous phase using smaller concentrations of **1a** in 1.00 mM hydrochloric acid [$(C_{\mathbf{1a}})_o$ = *ca.* 3.1 mM] and also with a more concentrated solution (23.1 mM) in 1.00 mM hydrochloric acid in the presence of sufficient amount of dioxane (*ca.* 10%) for solubilization. Spectra recorded with homogeneous solutions had identical features with these recorded with the suspension described earlier. Similar signals were also observed in the ^{31}P NMR spectra of a suspension of **1a** (17 mg) in 3 mL of water after 15 hr of signal accumulation. The parent signal of **1a** could be observed separately at

-1.9 ppm in aqueous solutions only when a large excess of 1a was added to the above suspension.

The ^{31}P NMR spectra of suspensions (17 mg in 3 mL) (and also homogeneous solutions – *ca.* 3.1 mM) of esters 1b and 1c in 1.0 mM hydrochloric acid were observed after signal accumulation from 1 to 15 hr (Table V, Plate X and XI). Ester 1b gave the following signals: a quintet at -1.92 ppm (parent carbonyl form resulting from the insoluble portion?), quintets at -0.65 ppm and +17.56 ppm (intermediates probably from 39b and 40b) and a doublet of quintets at +11.3 ppm ($^1J_{PH}$ = 720 Hz) (3). The area ratio for signals corresponding to 40b and 39b was found to be 1.32 (corresponding to *ca.* 43% reaction calculated from peak area ratios after 15 hr pulsing). Ester 1c gave the following signals: a quintet at -1.4 ppm (parent carbonyl form resulting from the insoluble portion?), quintets at 0.0 ppm and +18.12 ppm (intermediates probably from 39c and 40c) and a doublet of quintets (weak) at 11.53 ppm ($^1J_{PH}$ = 730 Hz) (3). The area ratio for signals corresponding to 40c and 39c was found to be 0.31 (corresponding to *ca.* 11% reaction calculated from peak area ratios after 15 hr pulsing). When the spectra were observed on completely homogeneous solutions (*ca.* 3.0 mM) of 1b or 1c in 1.0 mM hydrochloric acid (instead of a suspension after pulsing for 15 hr), all the features described above were displayed except for the fact that the signals at -1.92 ppm (1b) and at -1.4 ppm (1c) were not detected on the homogeneous solutions. However, the spectra observed from homogeneous solutions of 1b or 1c in 1.0 mM hydrochloric acid were noisy in spite of signal accumulation even after 15 hr.

The two additional signals (-0.3 and +17.9 ppm from 85% H_3PO_4) observed in acid solutions of 1a were certainly suggestive of some structural transformation, such as hydration of 1a in solution by a comparatively fast process. Unfortunately, no structurally related known intermediates could be found in the literature for comparison of ^{31}P signals or any other property. However, two signals appearing at -0.3 ppm and +17.9 ppm could be attributed to structures 39a and 40a (Scheme V), respectively. The assignment is supported by the data on the relative peak area ratios observed for the corresponding signals arising from esters 1a, 1b and 1c. The area ratios for 40a/39a = 1.17; 40b/39b = 1.64 and 40c/39c = 0.31. The decreasing order for the relative area ratios 40/39 [b. X = Cl; a. X = H; c. X = Me] is in harmony with the substituent effect observed for the stability of certain carbonyl hydrates.[64] The equilibrium constant for the reaction: below is, of course, defined as

$$\underset{55}{RR'C{=}O} + H_2O \rightleftharpoons \underset{56}{RR'C(OH)_2}$$

$K_{eq}[H_2O] = C_{55}/C_{56}$ and is given for a few carbonyl compounds in Table IX. It is clear from the data in Table IX that the electron-withdrawing Cl atom stabilizes the hydrate 56 whereas the electron-donating Me group has a destabilizing influence on the hydrate 56. Similarly, the electron-withdrawing Cl atom could stabilize the carbonyl hydrated form, as in 40b, compared to that in 40a and that in 40c. The ^{31}P signal corresponding to the carbonyl hydrated form 40 should be predominant over that for the phosphonyl hydrated form 39 when the *p*-substituent is an electron-withdrawing group like Cl such as in 1b. When the *p*-substituent is an electron-donating group such as in 1c, the carbonyl hydrated form 40c would be expected to be less stable compared to 39c.

TABLE IX

EQUILIBRIUM CONSTANTS AT 25°C FOR 55 + $H_2O \rightleftarrows$ 56

Substituents		$K_{aq}[H_2O]^{64}$
R	R'	
H	Et	0.71
H	Me	1.3
H	$ClCH_2$	37
H	Cl_3C	2.8×10^4
Me	Me	2×10^{-3}
Me	Cl_2CH	2.9
$ClCH_2$	$ClCH_2$	10

Thus, judging from the relative area of the signals 40/39, the downfield signals appearing at +17.56 ppm, +17.9 ppm, and +18.12 ppm could be attributed to structures 40b, 40a and 40c, respectively. It is interesting that a positive value of ρ observed for a linear correlation between $E_{\frac{1}{2}}$ and σ^+ for similar diethyl p-substituted benzoylphosphonates including the esters 1a-c, has also been reported to be positive (+ 4.7).[16] A positive slope for the Hammett correlation between λ_{max} ($n \rightarrow \pi^*$) and σ^+ has also been recorded.[92] The decreasing stability of the carbonyl hydrate 40, as the substituent is varied on the arene ring from Cl to H to Me, parallels the reactivity of the carbonyl group in esters 1a-c. The stability of the hydrates 40a-c and the reactivity of the carbonyl group in 1a-c may both arise from the same cause, i.e., polarization of the carbonyl group in the esters 1a-c. The transition state in the base-catalyzed hydrolysis may look more like the hydrate.

Assignment of the structures 39a, 39b and 39c to signals appearing at -0.3 ppm, -0.65 ppm and 0.0 ppm, respectively, seems justified from the comparison with signals found for H_3PO_4.

Considering the case of ester 1a, the two signals appearing at -0.3 ppm and +17.9 ppm were observed when 1a was dissolved in hydrochloric acid or in water and the ^{31}P NMR spectra were recorded immediately after dissolution and after pulsing for 1 hr. Signals from ^{31}P NMR spectra were observed from a suspension of 1a in water (17 mg in 3 mL) after t_o + 5 min. After pulsing the suspension in water for 60 min, only two predominant signals were observed from this solution at -0.3 ppm and +17.9 ppm, tentatively assigned to intermediates 39a and 40a. Signals arising from 3 could also be detected even though partially obscured in the noise. When a large additional quantity of ester 1a was added to the above suspension (after t_o + 65 min), another additional signal appeared at -1.9 ppm (after pulsing for 10 min) and was considered to arise from the free carbonyl form 1a from the undissolved state as reported previously. In order to rule out the possibility that the two original signals (-0.3 ppm and 17.9 ppm) might have originated from 3, excess ester 3 was added to the above suspension containing excess ester 1a in water (after t_o + 75 min). The spectrum was observed after pulsing for 10 min. The following signals were distinctly seen: +17.9 ppm (weak)(40a); -0.3 ppm (weak)(39a), -1.9 ppm (1a) and a predominant doublet centered at +11.3 ppm, $^1J_{PH}$ = 720 Hz (3) [see Table IV and Plate IX(A), IX(B) and IX(C)].

On the basis of the ^{31}P NMR data described above, the following protonation-hydration process for an aqueous acid solution of 1a seems reasonable as given in equilibria (12) and (13). Ester 1a could exist in equilibrium with a stable form 39a via a fast reaction:

$$1a + H_3O^+ \overset{K_{eq}}{\rightleftharpoons} 39a \tag{12}$$

Species 39a and 40a could also be in rapid equilibrium:

$$39a \overset{K'_{eq}}{\rightleftharpoons} 40a \tag{13}$$

The equilibrium (13) could be slow enough on the NMR time scale to result in the generation of separate signals. It would not be unreasonable to predict a stable structure like 39a to form in aqueous solutions of 1a since stable cyclic phosphorane systems[41,66,97] have been isolated. Also examples of pentavalent phosphorous intermediates in other solutions are becoming more common place.[55,73,96]

Modified Rate Equation From Scheme V

From the model described above, i.e., if an aqueous-acid solution of 1a exists as a rapid equilibrium mixture consisting of mostly 39a and 40a and a very small amount of free carbonyl form 1a, the observed phenominological rate would be given by Eq. (14):

$$\text{rate} = -\frac{d(C_{39a} + C_{40a})}{dt} \quad \text{or} \quad \frac{d\,C_{27a}}{dt} \tag{14}$$

In the steady state:

$$-\left(\frac{d(C_{39a} + C_{40a})}{dt}\right)_{ss} = \left(\frac{d\,C_{27a}}{dt}\right)_{ss} \tag{15}$$

In Scheme V (see page 64), if both path (A) and path (C) were assumed to be fast equilibria and path B to be the r.d. step, applying the equilibrium approximation,[30] the rate of reaction would be defined by Eq. (16) from a steady state approximation[11] with respect to 35a, where

$$\text{rate} = \left(\frac{dC_{27a}}{dt}\right)_{ss} = \frac{k_1 k_2\, C_{1a}\, C^n_{H_2O}}{(k_{-1} + k_2)} \tag{16}$$

n could have a value 2 or 3 depending upon the number of equivalents of water molecules involved in the intermediate 35a. Since C_{1a} would be controlled by equilibrium (12), one may write the concentration of 1a in terms of the concentration of 39a from Eq. (17):

$$C_{1a} = C_{39a}/K_{eq}\, C_{H_3O^+} \tag{17}$$

Combining Eqs. (16) and (17) we have:

$$\left(\frac{dC_{27a}}{dt}\right)_{ss} = \frac{k_1 k_2\, C_{39a}\, C^n_{H_2O}}{(k_{-1} + k_2)\, K_{eq}\, C_{H_3O^+}} \tag{18}$$

However, from equilibrium (13) we have

$$C_{40a} = K'_{eq}\, C_{39a} \tag{19}$$

and adding the term C_{39a} to Eq. (19) one would get the combined concentration of the species 39a and 40a from Eq. (20):

$$C_{39a} + C_{40a} = (K'_{eq} + 1)\, C_{39a} \tag{20}$$

Now, the rate of the reaction could be expressed in terms of the combined concentration of the equilibrium species 39a and 40a by Eq. (21) combining Eqs. (18) and (20):

$$\left(\frac{dC_{27a}}{dt}\right)_{ss} = \frac{k_1 k_2 \, C^n_{H_2O} \, (C_{39a} + C_{40a})}{(k_{-1} + k_2) \, K_{eq} \, (1 + K'_{eq}) \, C_{H_3O^+}} \qquad (21)$$

In the steady state, combining Eqs. (15) and (21), the rate equation reduces to Eq. (22).

$$-\left(\frac{d(C_{39a} + C_{40a})}{dt}\right)_{ss} = \frac{k_1 k_2 \, C^n_{H_2O} \, (C_{39a} + C_{40a})}{(k_{-1} + k_2) \, K_{eq} \, (1 + K'_{eq}) \, C_{H_3O^+}} \qquad (22)$$

Thus, from the above model the observed rate of decay in terms of total concentration of 39a and 40a $(C_{39a} + C_{40a})$ would be given by Eq. (23).

$$-\left(\frac{d(C_{39a} + C_{40a})}{dt}\right)_{ss} = k_{obs} \, (C_{39a} + C_{40a}) \qquad (23)$$

From Eq. (22) we have

$$k_{obs} = \frac{k_1 k_2 \, C^n_{H_2O}}{(k_{-1} + k_2) \, K_{eq} \, (1 + K'_{eq}) \, C_{H_3O^+}} \qquad (24)$$

and after factoring out pH and water dependence:

$$k'_{obs} = \frac{k_1 k_2}{(k_{-1} + k_2) \, K_{eq} \, (1 + K'_{eq})} \qquad (25)$$

Equation (23) would predict a rate law of 1st order in the combined species 39a and 40a which are in equilibrium and also a dependence of

k_{obs} by Eq. (26) below. That is, from Eqs. (24) and (25), we find:

$$k'_{obs} = k_{obs} \, C_{H_3O^+}/C^n_{H_2O} \tag{26}$$

Thus Eq. (9) (see page 68) using Scheme III (see page 26) is equivalent to Eq. (22) using Scheme V (see page 64) for a solution at constant pH. That is, both Eqs. (9) and (22) have identical mathematical forms with appropriate concentration terms, [C_{1a} in Eq. (9) and ($C_{39a} + C_{40a}$) in Eq. (22)] and appropriate rate constants at constant pH. However, Eq. (22) explicitly describes the pH dependence of k_{obs} and is based on additional evidence from ^{31}P NMR analysis.

Modified Mathematical Expression for Absorbance of Ester **1a** in Aqueous Solutions

If the observed absorbance of **1a** in aqueous-acid solutions is assumed to be from **1a**, **39a**, and/or **40a** existing in a rapid equilibrium and **27a** produced in a stoichiometric amount from **1a**, the absorbance of the solution at time t would be given by Eq. (27), the factor ℓ is not

$$\begin{aligned}(A_T)_t = {} & \varepsilon_{39a} (C_{39a})_t + \varepsilon_{40a} (C_{40a})_t \\ & + \varepsilon_{1a} (C_{1a})_t + \varepsilon_{27a} (C_{27a})_t \end{aligned} \tag{27}$$

explicitly included in Eq. (27), since ℓ=1 cm in all the experiments. Expressing the concentration of equilibrium species **1a** and **40a** in terms of concentration of **39a** (C_{39a}) and combining Eqs. (17), (19) and (27) we have

$$(A_T)_t = \varepsilon_{\mathbf{39a}} (C_{\mathbf{39a}})_t + \varepsilon_{\mathbf{40a}} K'_{eq} (C_{\mathbf{39a}})_t + \varepsilon_{\mathbf{1a}} (C_{\mathbf{39a}})_t / K_{eq} C_{H_3O^+} + \varepsilon_{\mathbf{27a}} (C_{\mathbf{27a}})_t \qquad (28)$$

or

$$(A_T)_t = \varepsilon' (C_{\mathbf{39a}})_t + \varepsilon_{\mathbf{27a}} (C_{\mathbf{27a}})_t \qquad (29)$$

where

$$\varepsilon' = \varepsilon_{\mathbf{39a}} + K'_{eq} \varepsilon_{\mathbf{40a}} + \varepsilon_{\mathbf{1a}} / K_{eq} C_{H_3O^+} \qquad (30)$$

One might reasonably assume $\varepsilon_{\mathbf{40a}} << \varepsilon_{\mathbf{39a}}$ since in **40a** the π-bond in the C=O group has been formally destroyed or at least significantly altered. Also, one could assume $\varepsilon_{\mathbf{1a}} \approx \varepsilon_{\mathbf{39a}}$ since in both **1a** and **39a** 2pπ-3dπ overlap is possible which is believed to be the cause of the optical absorption.[26,63,92] If the value of K_{eq} for the equilibrium in Eq. (12) is assumed to be of the order of 10^6, the factor $\varepsilon_{\mathbf{1a}}/K_{eq} C_{H_3O^+}$ is about

$$\mathbf{1a} + H_3O^+ \overset{K_{eq}}{\rightleftharpoons} \mathbf{39a} \qquad (12)$$

0.01 $\varepsilon_{\mathbf{1a}}$ in a solution of pH 4 (the contribution of $\varepsilon_{\mathbf{1a}}$ would still be smaller at lower pH). The above assumption seems justifiable in the light of ^{31}P NMR data for the aqueous suspension of **1a** described earlier. Under the conditions assumed above, i.e., $C_{\mathbf{1a}} << C_{\mathbf{39a}}$, Eq. (30) will reduce to Eq. (31)

$$\varepsilon' \approx \varepsilon_{\mathbf{39a}} \qquad (31)$$

and Eq. (29) will reduce to Eq. (32):

$$(A_T)_t \simeq \varepsilon_{\mathbf{39a}} (C_{\mathbf{39a}})_t + \varepsilon_{\mathbf{27a}} (C_{\mathbf{27a}})_t \qquad (32)$$

Expressing the absorbance in terms of the total concentration of the equilibrium species $(C_{39a} + C_{40a})$, combining Eqs. (20) and (32) we have:

$$(A_T)_t \approx \left[\frac{\varepsilon_{39a}}{(1 + K'_{eq})}\right] (C_{39a} + C_{40a}) + \varepsilon_{27a} (C_{27a})_t \qquad (33)$$

If 39a and 40a are assumed to be produced from a solution of 1a instantaneously with very small amount of 1a remaining in solution, then:

$$(C_{39a} + C_{40a})_{t \to o} \approx (C_{1a})_o \qquad (34)$$

Since 27a is assumed to be produced from an equilibrium mixture of 39a and 40a, from stoichiometry and mass balance we have:

$$(C_{39a} + C_{40a})_t + (C_{27a})_t + (C_{1a})_t = (C_{1a})_o \qquad (35)$$

If $(C_{1a})_t << (C_{39a} + C_{40a})_t$ as explained previously, Eq. (35) can be rewritten as

$$\left[(C_{39a} + C_{40a})_t + (C_{27a})_t\right] \approx (C_{1a})_o \qquad (36)$$

and

$$(C_{27a})_t \approx (C_{1a})_o - (C_{39a} + C_{40a})_t \qquad (37)$$

Combining equations (33) and (37) one would obtain Eq. (38)

$$\begin{aligned}(A_T)_t \approx {} & \left[\frac{\varepsilon_{39a}}{(1 + K'_{eq})}\right] (C_{39a} + C_{40a})_t \\ & + \varepsilon_{27a}\left[(C_{1a})_o - (C_{39a} + C_{40a})_t\right]\end{aligned} \qquad (38)$$

and solving for $(C_{39a} + C_{40a})_t$, we have:

$$(C_{39a} + C_{40a})_t \simeq \frac{(A_T)_t - \varepsilon_{27a}\,(C_{1a})_o}{(\varepsilon_{39a}/1 + K'_{eq}) - \varepsilon_{27a}} \qquad (39)$$

Mathematically, Eq. (39) and Eq. (4) (see page 67) have identical forms. The Eq. (4) becomes identical with Eq. (39) if C_{1a} in Eq. (4) (obtained on the basis of Scheme III, page 26) is replaced by $(C_{39a} + C_{40a})$, and ε_{1a} in Eq. (4) is also replaced by $(\varepsilon_{39a}/1 + K'_{eq})$. Equation (22) (see page 86) and Eq. (39) could be rewritten in terms of the substrate concentration $(C)_t$ where $(C)_t = (C_{39a} + C_{40a})_t$. Considering the hydrolysis reaction in terms of decomposition of the equilibrium mixture of 39a and 40a of total concentration = $(C)_t$, we have from Eq. (22) reducing to Eq. (40)

$$-\left(\frac{d(C)_t}{dt}\right)_{ss} = k_{obs}\,(C)_t \qquad (40)$$

where k_{obs} is given by Eq. (24). Equation (41) would be the integrated form of Eq. (40):

$$-\log_e (C)_t = -\log_e (C)_o + k_{obs}t \qquad (41)$$

If $(C_{39a} + C_{40a})_t$ is written as the combined substrate concentration $(C)_t$, from Eq. (39), we have

$$(C)_t = \frac{(A_T)_t - \varepsilon_{27a}\,(C_{1a})_o}{\varepsilon_1 - \varepsilon_{27a}} \qquad (42)$$

where $\varepsilon_1 \equiv \left(\varepsilon_{39a}/(1 + K'_{eq})\right)$ would be the extrapolated molar absorptivity of 1a in aqueous solutions at $t \to o$. Equations (40), (41) and (42) obtained from Scheme V are identical in their mathematical forms to Eqs. (9), (10) and (4) obtained from Scheme III. (See pages 67,68 and 26 for these equations and Schemes).

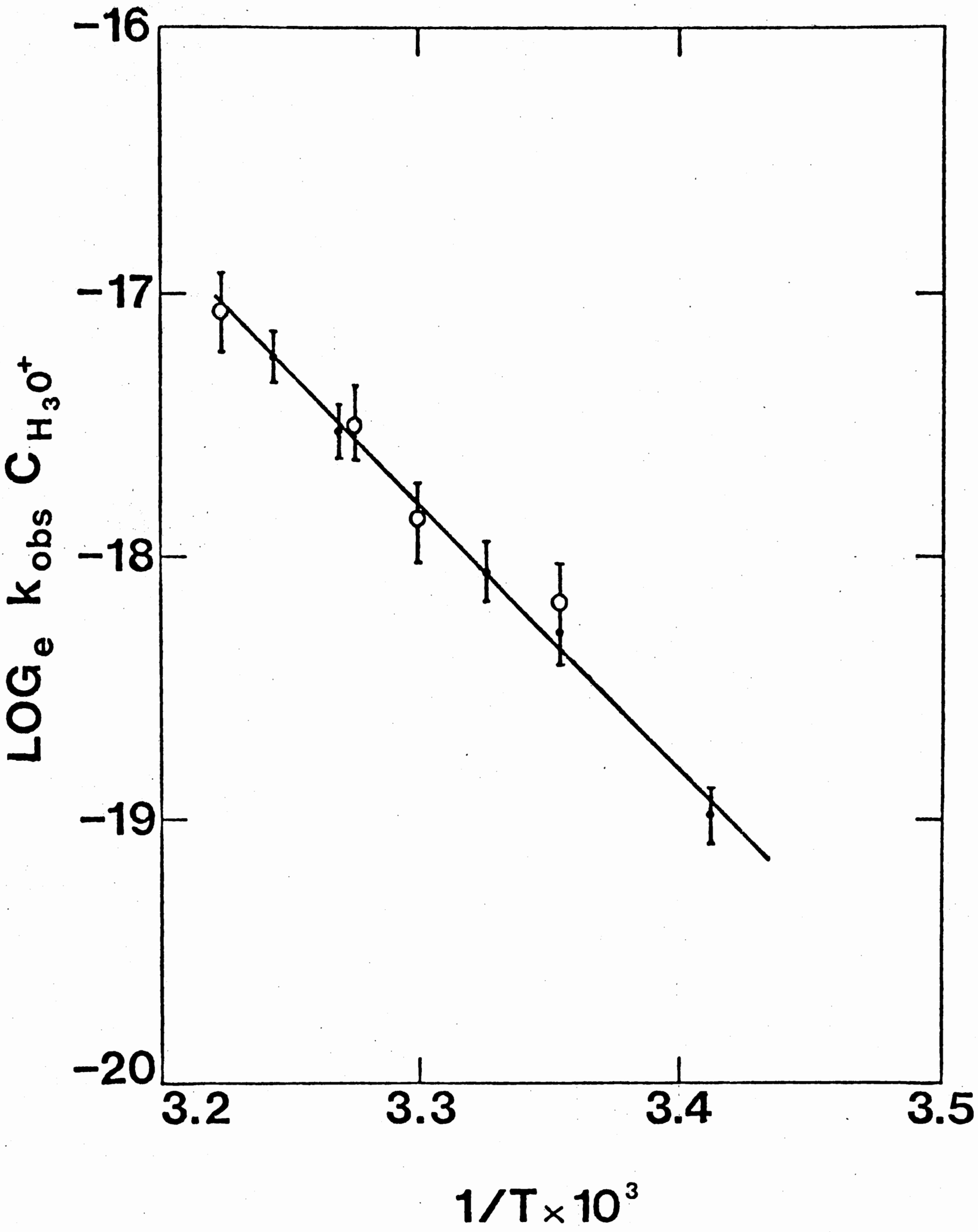
Analysis of Kinetic Results Based on Scheme V

The observed rate constant k_{obs} evaluated from Eq. (22) or (40) or from their equivalent forms, Eqs. (4) and (9), would be the experimental pseudo first-order rate constant for either case where n = 2 or 3. Thus we cannot eliminate the possibility of formation of a hydrate from $\underset{\sim}{1a}$ and water and which involves two equivalents of water as in $\underset{\sim}{35a}$ in the r.d. step (Scheme III). There is evidence for three equivalents of water participating in the hydration of 1,3-dichloroacetone as cited previously.[6,7,8,31] However, we could not find an example which was analogous (in the sense that two adjacent groups, -C=0 being one of them, were electron withdrawing and promoted hydration of C=0 group) and had two equivalents of bound water confirmed for the hydrate structure.

An Arrhenius plot for the rate constant $k_{obs}\ C_{H_3O^+}$ can be found in Figure 7. Similar values of rate constants were estimated for aqueous solutions at different temperatures, using the experimental average pH values and neglecting the initial higher rate observed in these solutions during the first 10-15% of the reaction time. These data points also fall nearly on the line obtained for the Arrhenius plot for acid solutions (Figure 7). A value for $\Delta H^{\ddagger}$ was found to be 20 ± 2 kcal mol^{-1} and the limiting values of $\Delta S^{\ddagger}$ was estimated to be -44 ± 7 eu for n = 2 and -52 ± 7 eu for n = 3 in Eq. (22). High negative values for entropy

Figure 7. Arrhenius Plot for the Hydrolysis of Ester **1a** in Aqueous HCl (●) at pH = 3.6 ± 0.03.

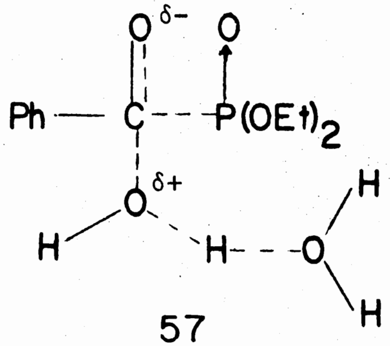
(○) represents data points calculated from data for hydrolysis of **1a** in water and the experimentally observed pH = 4.4.



-16
-17
-18
-19
-20
3.2
3.3
3.4
3.5
LOG$_e$ K$_{obs}$ C$_{H_3O^+}$
1/T × 10^3

of activation is certainly in conformity with a cyclic transition state for formation of 35a in the rate-controlling step (Scheme III and Scheme V).

The exact number of water molecules involved can only be determined by evaluating the order with respect to water for the uncatalyzed reaction. Potentially, one might attempt to determine the rate constants for the hydrolysis of 1a in an inert solvent like dioxane and add known amounts of water. However, the reaction rate (monitoring the $n \rightarrow \pi^*$ band) for the hydrolysis of 1a even in 1:1 water-dioxane mixture was found to be too slow [only 10% change was noted in the absorbance of a more concentrated solution (4.72 mM) after 37 hr] for accurate measurements to be made, and direct evaluation of n was therefore not feasible. Even though the exact equivalents of water molecules involved in the intermediate 35a is not known accurately, it is reasonable that at least two equivalents of water participate, one of the water molecules acting as a nucleophile and the other acting as a general base and for an effective proton transfer to the carbonyl group. If the second molecule of water were to act as a general base without the oxygen of the C=O group being involved (leading to a linear transition state) as shown, in 57, one would expect a *high* primary isotopic effect. On the other hand, if



57

the proton of the water solvent matrix were to be linked to the carbonyl oxygen to give a cyclic transition state leading to the intermediate 35, the primary isotopic effect would be reduced.[21] The gross isotopic effect for the hydrolysis of 1a in water and D_2O was observed to be 1.6 at 25°C as stated previously. Consequently, the gross isotopic effect would be a total result due to L_3O^+, LO^- and L_2O where L = H or D and these *factors are not separable*. Also other nonspecific effects due to differences in viscosity of H_2O and D_2O could add to the isotope value.[49] Any positive mechanistic conclusions based on gross solvent isotopic effect alone should be made with much caution.

Equilibrium Constant for 39a $\rightleftarrows$ 40a

Assuming that the ester 1a exists as an equilibrium mixture of 39a and 40a in aqueous acid solutions, the absorbance of an aqueous acid solution of 1a at t→o would be given by:

$$[(A)_{t\to o}]_{aq} = \varepsilon_{39a}(C_{39a})_o + \varepsilon_{40a}(C_{40a})_o \tag{43}$$

Since 40a has no formal π bond and $\varepsilon_{40a} << \varepsilon_{39a}$, then Eq. (43) reduces to:

$$[(A)_{t\to o}]_{aq} \simeq \varepsilon_{39a}(C_{39a})_o \tag{44}$$

Recalling Eqs. (20) and (34) we have:

$$C_{39a} + C_{40a} = (1 + K'_{eq})\, C_{39a} \tag{20}$$

$$(C_{39a} + C_{40a})_{t\to o} \approx (C_{1a})_o . \tag{34}$$

If the equilibrium is assumed to be rapid such that the species **39a** and **40a** attain equilibrium instantaneously, in the limit as t→o, Eq. (20) can be written as:

$$(C_{\underset{\sim}{39a}} + C_{\underset{\sim}{40a}})_{t\to o} = (1 + K'_{eq})\,(C_{\underset{\sim}{39a}})_o \qquad (35)$$

Combining Eqs. (34), (35) and (44) one would get Eq. (45) for the absorbance of **1a** in aqueous solution as t→o.

$$[(A)_{t\to o}]_{aq} \approx \frac{\varepsilon_{\underset{\sim}{39a}}\,(C_{\underset{\sim}{1a}})_o}{(1 + K'_{eq})} \qquad (45)$$

In a solution of **1a** in an inert nonaqueous solvent such as hexane, assuming that **1a** exists in the free carbonyl form, absorbance is given by Eq. (46):

$$[(A)_o]_{hexane} = \varepsilon_{\underset{\sim}{1a}}\,(C_{\underset{\sim}{1a}})_o \qquad (46)$$

Now, in both structures **1a** and **39a**, 2pπ-3dπ overlap is possible and it is reasonable to assume that:

$$\varepsilon_{\underset{\sim}{1a}} \approx \varepsilon_{\underset{\sim}{39a}}$$

Now $\varepsilon_{\underset{\sim}{1a}}$ and $\varepsilon_{\underset{\sim}{39a}}$ can be obtained via Eqs. (46) and (45), respectively. Combining the above Eq. with Eqs. (45) and (46), we get Eq. (47) for

$$[(A)_o]_{hexane}/[(A)_{t\to o}]_{aq} \approx 1 + K'_{eq} \qquad (47)$$

the evaluation of equilibrium constant K'_{eq}.

When $(C_{\mathbf{1a}})_o$ = 1 M, Eq. (47) reduces to Eq. (48). Thus K'_{eq} can be

$$[(\varepsilon)_o]_{hexane}/[(\varepsilon)_{t\to o}]_{aq} \simeq 1 + K'_{eq} \qquad (48)$$

calculated from the absorptivity of solutions of **1a** measured in hexane and aqueous acid. K'_{eq} could also be evaluated from the peak area ratios of the corresponding ^{31}P NMR signals postulated as arising from **39a** and **40a** in the ^{31}P NMR spectra of a solution of **1a** in aqueous hydrochloric acid (pH ≈ 3.0). The values calculated from absorbance readings and ratio of areas under the ^{31}P NMR signals are tabulated in Table X.

TABLE X

EQUILIBRIUM CONSTANT FOR **39a** $\rightleftarrows$ **40a** IN AQUEOUS HYDROCHLORIC ACID (pH = 3.0) AT ROOM TEMPERATURE (*ca.* 30°C)

Log ε for **1a**		K'_{eq} Calculated from	
Hexane	Aqueous HCl (pH = 3.0)	ε Values	^{31}P NMR Signals
4.10	3.73	1.33	1.17 (35%)[a] 1.21 (82%)[a]

[a] Percentage denotes the fraction of the reaction at which the area ratios were measured.

It can be seen from Table X that the calculated K'_{eq} from ε values corresponds reasonably well to the K'_{eq} obtained by the integration of areas under the ^{31}P NMR signals (in spite of the assumption that $\varepsilon_{1a} \approx \varepsilon_{39a}$). This observation lends credence to our postulate that the intermediates 39a and 40a are formed rapidly from 1a and are the precursors of the products identified, and equilibrium between 39a and 40a is maintained throughout the course of the reaction. K'_{eq} calculated from ^{31}P NMR analysis may have some inaccuracies because of unknown NOE effects which are reported in phosphorus system.[42,47,100] The ^{31}P NMR signals were obtained from an aqueous suspension of 1a (17 mg in 3 mL) of hydrochloric acid (pH ≈ 3.0) after signal accumulation for 15 hr with 15 sec as delay time between pulses. It was assumed that a duration of 14 sec would be long enough to permit relaxation of the nuclei so that the integrated areas under the ^{31}P NMR signals could be a measure of the relative concentrations. Even with a delay time of 40 sec, the area ratio was not altered. ^{31}P NMR data were also examined on dilute solutions of 1a and identical results were obtained.

Summary of Significance of the Research

In summary, hydrolysis of diethyl benzoylphosphonate (1a) in aqueous and aqueous hydrochloric acid solutions has been found to be pseudo first-order in 1a. Rate retardation was observed in acid solutions and the pseudo first-order rate constant was found to be inversely proportional to the acid concentration in solution. The above observation would exclude the possibility of an $A_{AC}1$ or $A_{AC}2$ type of mechanism being operative with the $P(O)(OEt)_2$ moiety as the leaving group.

The proposed mechanism for the hydrolysis of ester 1a involves the attack by two or three equivalents of water on 1a leading to a cyclic hydrate intermediate 35a in the r.d. step. The intermediate can collapse by an intramolecular proton abstraction by the P=0 group in a fast step resulting in the C-P bond cleavage. Although the exact number of water molecules (n = 2 or 3) involved in the r.d. step could not be unequivocally evaluated from the present study, a large negative entropy of activation [$\Delta S^{\ddagger}$ = 52 ± 7 eu (n = 3)] and low solvent isotopic effect [$k_{(H_2O)}/k_{(D_2O)}$ = 1.6] observed for the hydrolysis of 1a would support the formation of the proposed cyclic hydrate intermediate 35a.

On the basis of UV, Raman and ^{31}P NMR spectral data from solutions of 1a, it is proposed that in aqueous-acid solutions hydration occurs at both the C=0 and P=0 groups. Ester 1a could exist in an equilibrium mixture with the two hydrated forms 39a and 40a. The above model also accounts for the observed phosphonyl ester cleavage in highly acidic solutions and which involves nucleophilic attack of water on phosphorus.

CHAPTER III

EXPERIMENTAL

General Data

Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. The boiling points recorded are uncorrected. The refractive indices reported were measured at room temperature using a Bausch and Lomb Abbe Refractometer. Details of the instrumentation used for recording various spectra are summarized under the sub-heading Instrumentation. The chemical shifts reported for ^{1}H NMR signals are in ppm from tetramethylsilane (TMS) as internal standard. ^{31}P NMR signals reported are in ppm from 85% H_3PO_4 as external standard. The symbolism + δ values mean downfield from the standard and - δ values mean upfield from the standard.

Materials

Benzoic acid (27a) [Baker Analyzed], reagent grade, was used without further purification; m.p. 122.5-123.0°C. Diethyl hydrogenphosphonate (3) [Aldrich], reagent grade, was used without further purification; b.p. 70°C/11 mm. Dioxane [Mallinckrodt], reagent grade, was used after boiling over lithium aluminum hydride (LAH)[5] overnight under nitrogen (N_2) and was distilled over LAH and while flushing with dry nitrogen. The freshly distilled dioxane (b.p. 99.0-99.6°C/*ca.* 750 mm) was stored over Linde molecular sieve 3A. Purified dioxane was found to be free from peroxide as indicated by KI test.[35]

Deuterium oxide (Aldrich), gold label quality, containing 99.8 atom percent deuterium was obtained. A fresh sample was used for each kinetic run performed in D_2O. Hexane (Mallinckrodt-chrom AR grade; b.p. 68.7°C) was used without further purification as the solvent for obtaining the UV spectra of the esters.

Concentrated hydrochloric acid (Fischer Scientific), reagent grade, was used for successive dilution with distilled water to yield a stock solution (~ 0.1 N). The concentration of the hydrochloric acid solution was checked periodically by titration with standard sodium hydroxide. The latter was standardized against potassium acid phthalate as primary standard[83] using phenolphthalein as indicator. Potassium hydrogen phthalate (Mallinckrodt), analytical reagent grade, was used as the primary standard after it was dried at 110-115°C for 1-2 hr.[83] Sodium hydroxide (Fischer Scientific) reagent grade, standardized N/5 solution was used as stock solution. Distilled water (freshly distilled and cooled) was used for the kinetic runs which were also made in deionized water. The results were identical with those obtained, regardless of which type of water was used.

Preparation of Diethyl Benzoylphosphonate (1a)

A sample of diethyl benzoylphosphonate (1a) was prepared according to the method of Berlin and Taylor[17] and was used after vacuum distillation (twice); [b.p. 116-118°C/(0.15-0.2 mm), n_D^{24} = 1.5080., lit.[22,27] 141°C/2.5 mm; n_D = 1.5084]. ^1H NMR, ^{31}P NMR and IR spectral analysis of the sample was found to be identical with those of an authentic sample.

TLC analysis with 0.2 mm silica gel, using 1:9 acetone-chloroform mixture as solvent system, with I_2 as developer showed only one spot (R_f = 0.71). The ester was stored in a colored bottle over anhydrous $CaCl_2$. During the period of kinetic study, 5% decomposition was detected via a change in absorbance readings [from 1.285-1.225 for a solution of 1a (0.2353 mM) in 1.06 mM hydrochloric acid] over a period of six months.

Preparation of Diethyl p-Chlorobenzoylphosphonate (1b)

This compound was prepared according to a published procedure.[17] Freshly distilled p-chlorobenzoyl chloride [(6.1 g, 0.035 mol) (Aldrich) b.p. 148-149°C/cz. 15 mm], was charged in a 100 mL, three-necked flask fitted with a condenser, immersion thermometer and additional funnel (N_2 inlet) and was kept in a N_2 atmosphere. Triethyl phosphite (6.9 g, 0.04 mol) (Aldrich), b.p. 150-153°C/740 mm, was added at a slow rate, so that the temperature did not rise above 25°C. The flask was cooled in ice during the period of addition. After the addition was completed, the mixture was stirred under N_2 for 16 hr. Distillation of the product yielded 6.5 g (67%) of 1b, b.p. (132-134°C/(0.15-0.2 mm); n_D^{24} = 1.5210; lit.[93] 159°C/0.2 mm; n_D = 1.5203.[27] The IR and NMR spectra were found to be identical with those of an authentic sample. TLC analysis with 0.2 mm silica gel using 1:9 acetone-chloroform mixture as solvent system and I_2 as developer showed only one spot (R_f = 0.72).

Purification of Diethyl *p*-Toluoylphosphonate (**1c**)

A sample was prepared by a method developed by earlier workers[48] and modified by Berlin and Taylor.[17] Vacuum distillation [b.p. 128-130°C/(0.1-0.2 mm); n_D^{24} = 1.5125; lit.[90] 123-124°C/0.05 mm] gave a highly pure sample. TLC analysis performed on 0.2 mm silica gel using 1:9 acetone-chloroform mixture as the solvent system and I_2 as developer showed only one spot (R_f = 0.75). IR and NMR data for **Ic** were not found reported in the literature but are summarized below. An IR spectrum of a neat sample gave the following characteristic frequencies: C=O 1650 cm^{-1}; P→O 1260 cm^{-1}; P-O-C (broad) 1020-1060 cm^{-1} (Plate XIII). ^{1}H NMR ($DCCl_3$) gave the following signals: 1.38 [triplet ($J_{H_aH_b}$ = 7 Hz), $C\underline{H}_3$(a), 6 H]; 2.41 [singlet, *p*-$C\underline{H}_3$(e), 3 H]; 4.28 [split quartet ($J_{H_aH_b}$ = 7 Hz), $C\underline{H}_2$(b), 4 H]; 7.30 [doublet ($J_{H_cH_d}$ = 8 Hz), $Ar\underline{H}$(d), 2 H]; 8.19 [doublet ($J_{H_cH_d}$ = 8 Hz), $Ar\underline{H}$(c), 2 H], see Plate XII. The ^{31}P NMR spectrum was recorded in dioxane and gave only one signal: -1.4 ppm [quartet ($^{3}J_{POCH}$ = 8 Hz)] from 85% H_3PO_4. See Plate XI(A).

Instrumental Methods

Infrared spectral data were obtained on a Beckman IR-5A unit. The UV spectra and absorbance readings for the various kinetic runs were recorded on a Cary Model-14 recording spectrophotometer. The ^{1}H and ^{31}P NMR data were obtained on a Varian XL-100(15) NMR spectrometer equipped with a Nicolet TT-100 PFT accessory operating at 100.1 MHz for ^{1}H analysis and 40.5 MHz for ^{31}P NMR analysis. Most ^{31}P NMR spectra were recorded in FT mode with delay time (D5) between pulses of 15 sec and pulse width (P2) of 11.8 μsec. The number of acquisitions varied from 36 to 3500 (signal accumulations ranging from 12 min to 15 hr) depending upon the concentration of the ^{31}P-containing species in solution. ^{31}P NMR data have been summarized in Table (IV). Laser Raman spectra were recorded using a Model 52, argon laser as a source, with a detector (Jarrell-Ash 20-100 dual monochromator) and with Hammer photon-counting accessories (with a photon count rate of 2×10^{3} sec^{-1} and slits of width 3 cm^{-1} each). Measurement of the pH of samples was achieved using a Corning Model 12 research pH meter with a Corning glass-reference Calomel combination electrode (Corning catalog No. 476021) and employing standard buffers for calibrations. Certified buffer tablets (pH = 2.0 ± 0.01, pH = 4.0 ± 0.01) supplied by Coleman Instruments, Inc., Maywood, Illinois, were used as standards.

Preliminary UV Spectral Analysis

The UV spectra of solutions of ester 1a in water and in hydrochloric acid (pH $\simeq$ 2) showed λ_{max} at 268 nm corresponding to a $\pi \rightarrow \pi^*$ transition (Figure 2, Table II, page 38 and page 28). This band was monitored for evaluation of the concentrations of absorbing species in ester 1a in aqueous and aqueous hydrochloric acid solutions and for following the rate of hydrolysis of ester 1a. A stoichiometric amount of benzoic acid (27a) was found to be produced resulting from the hydrolysis of 1a in aqueous solutions via UV spectral analysis. The UV spectra of a solution of 1a in water (0.235 mM) observed after about 10 half lives was found to match exactly with the spectra of an authentic standard solution of benzoic acid of the same concentration (Figure 2). An examination of the UV spectra of aqueous solutions of 1a and 27a, both in presence and in absence of externally added hydrochloric acid, indicated that at the wavelength λ = 268 nm used in the present work the absorbance A_{27a} arising from the stoichiometric amount of 27a produced from 1a can not be neglected. Evaluation of the concentrations of the absorbing substrate species from the experimentally measured absorbance $(A_T)_t$ at λ = 268 nm would require the value of the apparent molar absorptivity for the species arising from 1a $(\varepsilon_{1a})_{t \to o}$ or $[\varepsilon_{39a}/(1 + K'_{eq})]^a$, and the molar absorptivity for 27a, ε_{27a} to be determined in aqueous and various hydrochloric acid solutions of different concentrations (pH). For the sake of convenience, the quantities $(\varepsilon_{39a}/1 + K'_{eq})$ and ε_{27a} could be designated as ε_1 and ε_2, respectively, and these new notations will be used in future discussions. Both ε_1 and ε_2 were separately determined in aqueous and acid solutions at different initial concentrations of hydrochloric acid since the electronic spectra of 27a has been reported to be affected by pH.[50]

Evaluation of Molar Absorptivity of Benzoic Acid ε_2 or ε_{27a} in Water and Hydrochloric Acid Solutions at λ = 268 nm at 25°C

A standard solution was prepared by dissolving 0.1257 g of benzoic acid (27a) in 1000 mL of distilled water. The absorbance of the solution was measured using a matched 1 cm quartz UV cell (Fischer Brand Suprasil Cat. #14-385-902-C). Solvent alone was added to the reference cell. Absorbance readings were recorded at a fixed wavelength, λ = 268 nm, using a Cary UV recording spectrophotometer Model-14. Absorbance

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[a] In aqueous and aqueous acid solutions there is evidence to show that the free carbonyl form from ester 1a exists in a part equilibrium with the two hydrated forms 39a and 40a by a fast process (see Scheme V and Eq. (39) and Eq. (41) under Discussion section, p. 64 and 90).

for other standard solutions of different concentrations prepared from the stock solution of **27a** by suitable dilutions were also measured. The molar absorptivity was calculated from Beer-Lamberts equation:

$$A = \varepsilon \cdot \ell \cdot C \tag{49}$$

where A denotes the measured absorbance, ε the molar absorptivity, ℓ the path length (= 1 cm) and C is the molar concentration of the absorbing species. Note that ε was evaluated from the slope computed by a linear least squares analysis from data for C and A using Eq. (49). Standard solutions of **27a** were also prepared in hydrochloric acid solutions by dissolving appropriate amounts of **27a** and by successive dilution, and absorbance readings were recorded. Hydrochloric acid solutions used were: 0.106 mM; 0.265 mM; 0.530 mM; 0.795 mM; 1.06 mM; 5.0 mM; 10 mM. The molar absorptivity of **27a** in each of the above HCl solutions was computed as described above. Figures 8 and 9 summarize the absorbance data for solutions of benzoic acid (**27a**) in water and in hydrochloric acid solutions (0.106 mM; 0.265 mM; 0.530 mM; 0.795 mM; 1.06 mM; 5.0 mM and 10.0 mM) at λ = 268 nm and 25°C. The ε_2 values extracted from the above set of data can be found in Table III (p. 29).

Verification of Beer-Lambert Law With Respect to Ester **1a** in Aqueous and Hydrochloric Acid Solutions and Evaluation of Molar Absorptivity for **1a**

Since the ester **1a** underwent hydrolysis in aqueous solutions, ε_1 was determined indirectly by following the initial rate of decay of absorbance of a solution of **1a** in water. The initial rate was followed

Figure 8. Plots of Concentration of Benzoic Acid (27a) Versus Absorbance at λ = 268 nm in Aqueous and Hydrochloric Acid Solutions.

C°_{HCl} (mM)

(□) 0

(▲) 0.265

(o) 0.795.

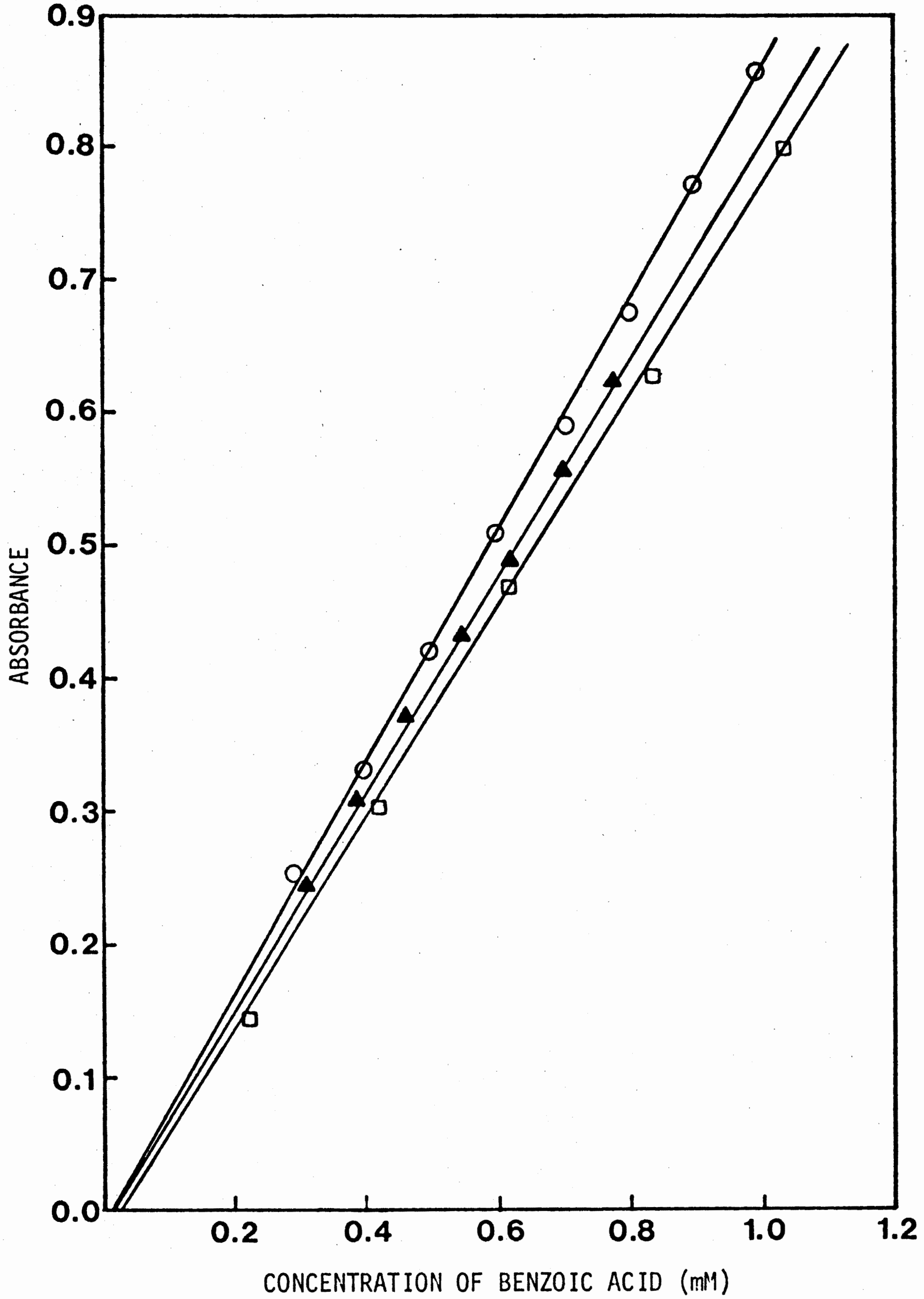

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
ABSORBANCE
0.2
0.4
0.6
0.8
1.0
1.2
CONCENTRATION OF BENZOIC ACID (mM)

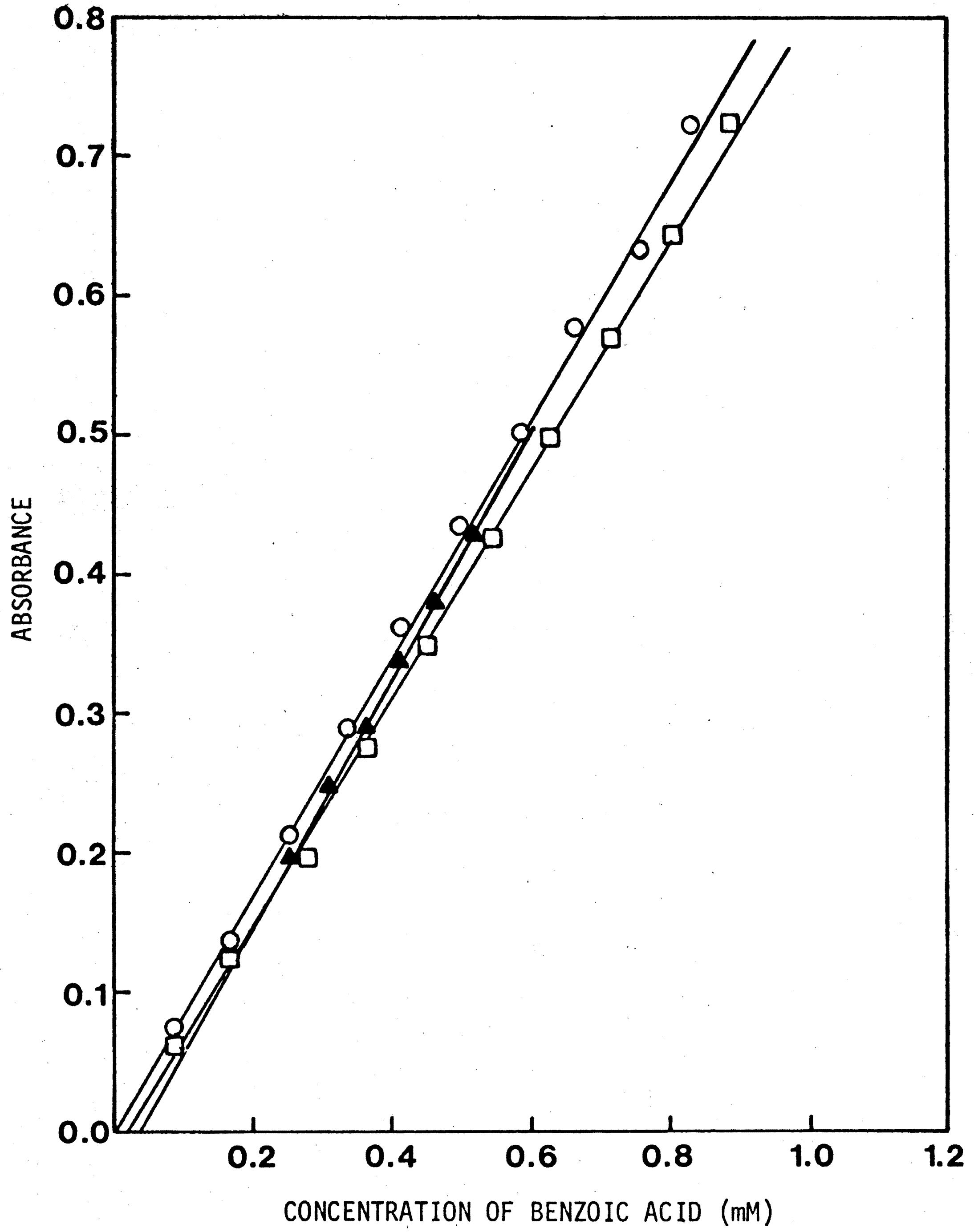
Figure 9. Plots of Concentration of Benzoic Acid (**27a**) Versus Absorbance at λ = 268 nm in Aqueous Hydrochloric Acid Solutions.

C°_{HCl} (mM)

(□) 0.106

(▲) 0.530

(o) 1.06


ABSORBANCE
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.2
0.4
0.6
0.8
1.0
1.2
CONCENTRATION OF BENZOIC ACID (mM)

up to 8% of reaction using various initial concentrations of **1a** (ranging from 0.140 to 0.235 mM). Initial rates of decay of absorbance at $\lambda = 268$ nm and 25 ± 0.1°C were measured for solutions of five different initial concentrations of **1a** (0.2353 mM; 0.2106 mM; 0.1879 mM; 0.1631 mM; 0.1404 mM). A sample of the ester **1a** (ranging from 5 µL to 3 µL) was withdrawn with a micro syringe from a vial and was placed in a previously weighed parafilm boat which was then weighed on a micro balance. The weighed sample of ester **1a** was dissolved (over a period of 60 sec.) in 100 mL of distilled water which was kept in a previously thermostated, stoppered Erlenmeyer flask. The temperature of the bath was maintained at 25 ± 0.1°C by using a Magniwhirl constant temperature system. The temperature of the UV cell was maintained by using a water-circulating pump with bath reservoir held at constant temperature (25 ± 0.1°C). The reaction mixture was withdrawn after $t_o + 100$ sec and was placed in a 1 cm quartz UV cell, and solvent alone was added to an identical reference cell. Absorbance $(A_T)_t$ readings were recorded for a period of 10 min on a Cary recording spectrophotometer Model-14 on a recording chart revolving at a constant speed of 1 div/20 sec. The wavelength was maintained at a constant value of $\lambda = 268$ nm throughout the measurements. Initial rates of decay of absorbance for the period $t_o + 120$ sec to $t_o + 540$ sec for aqueous solutions of ester **1a** with different initial concentrations $(C_{\mathbf{1a}})_o$, ranging from 0.2353 mM to 0.1404 mM, are given in Figure 10. For the extrapolation of absorbance of **1a** in water at $\lambda = 268$ mM at $t \to o$, a linear least squares fit between $-\log_e(A_T)_t$ and t for a pseudo first-order behavior was made and $(A_T)_{t \to o}$ was evaluated from the intercepts for each reaction mixture of known initial concentration. The linearity of the function $-\log_e(A_T)_t$

Figure 10. Initial Rate of Decay of Absorbance at λ = 268 nm for Solutions of Ester 1a in H_2O at T = 25 ± 0.1°C With Different Initial Concentration.

$(C_{1a})_o$ mM

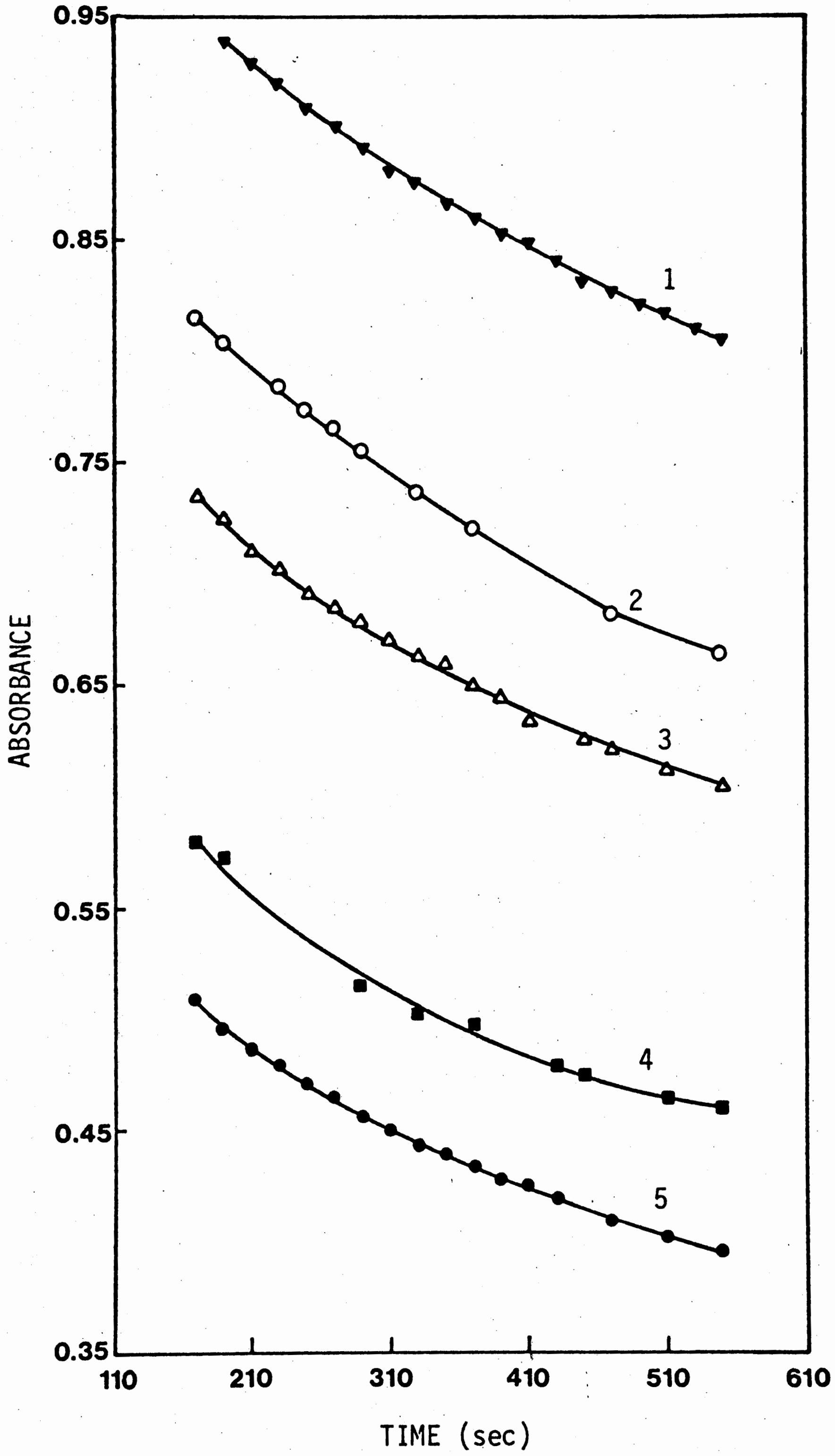
1) 0.2353

2) 0.2106

3) 0.1879

4) 0.1631

5) 0.1404


0.95
0.85
0.75
0.65
0.55
0.45
0.35
ABSORBANCE
110
210
310
410
510
610
TIME (sec)
1
2
3
4
5

versus t (up to 8% reaction) for aqueous solutions of 1a with different initial concentrations is provided in Figure 11. From the above procedure of linear extrapolation, the correlation coefficients (R^2) were found to be around 0.99 in most cases (see Table XI). This observation along with the fact that $\varepsilon_1 \approx 6\varepsilon_2$ (see Table II, page 28) indicated

TABLE XI

ABSORBANCE $(A_T)_o$ DATA EXTRAPOLATED FROM INITIAL RATES FOR SOLUTIONS OF DIETHYL BENZOYLPHOSPHONATE (1a) IN WATER FOR DIFFERENT INITIAL CONCENTRATIONS $(C_{1a})_o$ AT λ = 268 NM AND T = 25 ± 0.1°C

Initial Concentration of 1a $(C_{1a})_o$ mM	Absorbance Extrapolated to $t \to o$ $(A_T)_o^a$	Least Squares Correlation Coefficient R^{2a}	$k^a_{initial} \times 10^4$ sec^{-1}
0.2353	1.031	0.998	5.02
0.2106	0.905	0.999	6.22
0.1879	0.809	0.984	5.98
0.1631	0.664	0.972	8.16
0.1404	0.576	0.990	7.92
0.0	0.0	--	--

[a] Values of $(A_T)_o$, $k_{(initial)}$, and the least squares correlation coefficient, R^2 corresponding to each value of $(C_{1a})_o$ were obtained from individual least squares analysis on data presented in Figure 11, using the equation $-\log_e(A_T)_t = t\,k_{(initial)} - \log_e(A_T)_o$ in which $k_{(initial)}$ = slope and $-\log_e(A_T)_o$ = intercept.

Figure 11. Extrapolation of Absorbance at λ = 268 nm and T = 25 ± 0.1°C for t→0 for Solutions of Ester **1a** in H_2O With Different Initial Concentration.

$(C_{\mathbf{1a}})_o$ mM

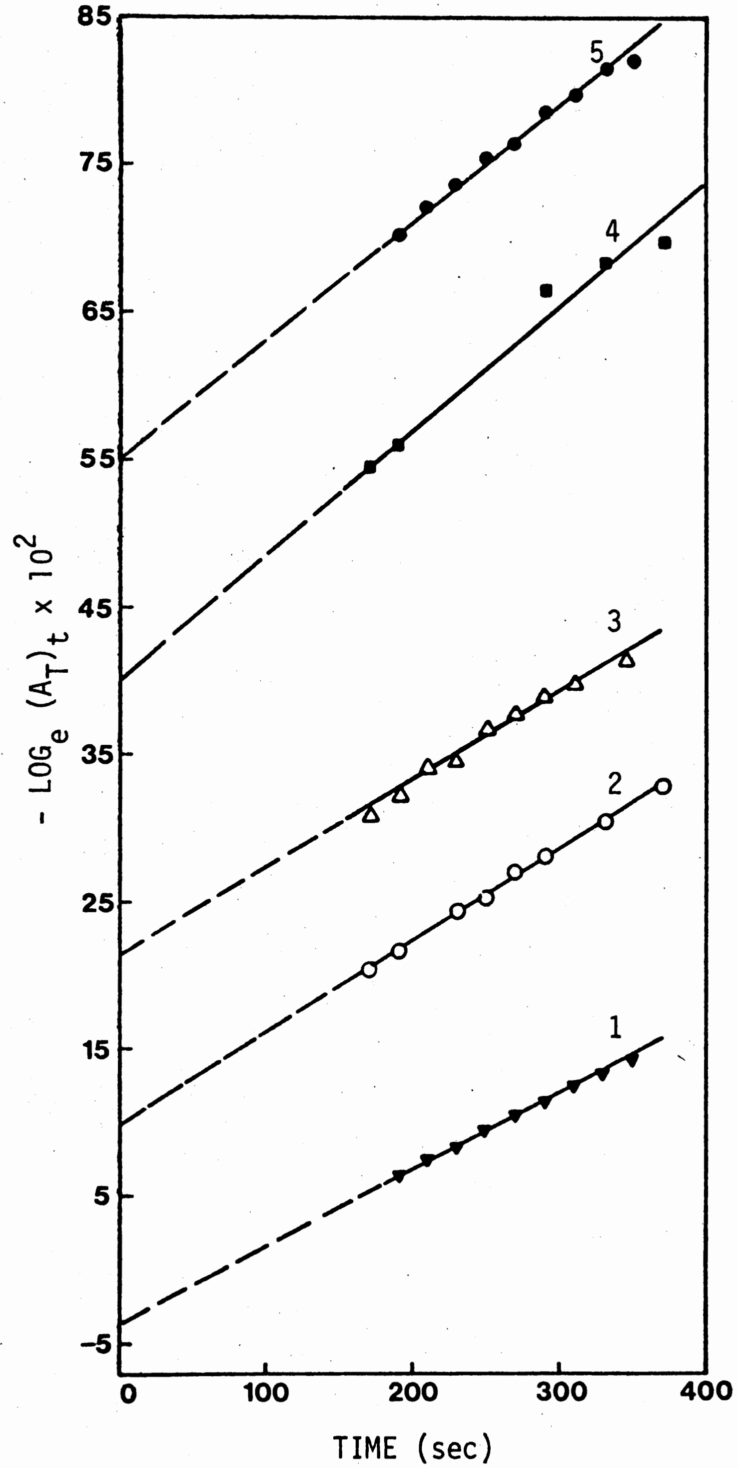
1) 0.2353

2) 0.2106

3) 0.1879

4) 0.1631

5) 0.1404


85
75
65
55
45
35
25
15
5
-5
0
100
200
300
400
- LOG$_e$ (A$_T$)$_t$ x 10^2
TIME (sec)
5
4
3
2
1

that the absorbance arising from the stoichiometric amount of **27a** produced from **1a** was negligible (calculated to be within 1-2% of the absorbance contributed by **1a**) for the above period (8%) of the reaction time. Values of $(A_T)_o$ thus obtained for solutions of different initial concentrations $(C_{\mathbf{1a}})_o$ aregiven in Table XI. Thus, ε_1 was evaluated from the following Eq. (50) applying the least squares fit procedure.

$$(A)_o = \varepsilon_1 (C_{\mathbf{1a}})_o \, \ell \qquad (50)$$

These values of $(A_T)_o$ were found to obey the Beer-Lambert Law, as can be judged from the linearity of the plot between $(A_T)_o$ and $(C_{\mathbf{1a}})_o$ shown in Figure 12. The values of ε_1 and the corresponding R^2 values were assessed and found to be

$$(\varepsilon_1)_{H_2O} = 4349 \ M^{-1} \ cm^{-1}; \text{ and } R^2 = 0.997.$$

Values of ε_1 for ester **1a** from various hydrochloric acid solutions were similarly evaluated. Validity of the Beer-Lambert Law for solutions of **1a** in hydrochloric acid was also verified as follows. Since hydrolysis of **1a** in hydrochloric acid was found to be slow, values of ε_1 were also evaluated from measurements of the absorbance of ten different standard solutions of **1a** (concentrations ranging from 0.0235 mM to 0.235 mM) in a standard hydrochloric acid solution (0.265 mM) as a test case.

Absorbance of the standard solutions of **1a** were measured within 10 min (t_o + 25 min to t_o + 35 min) in each case. Figure 13 represents a plot of such readings of absorbance [$(A)_t$ recorded after t_o + 30 min] versus initial concentration of **1a** in 0.265 mM hydrochloric acid. The linearity of the curve and hence the validity of Beer-Lambert Law is

Figure 12. Verification of Beer-Lambert Law, Plot of Initial Concentration of Ester 1a in Water Versus Absorbance at λ = 268 nm and T = 25 ± 0.1°C Extrapolated at t→0.

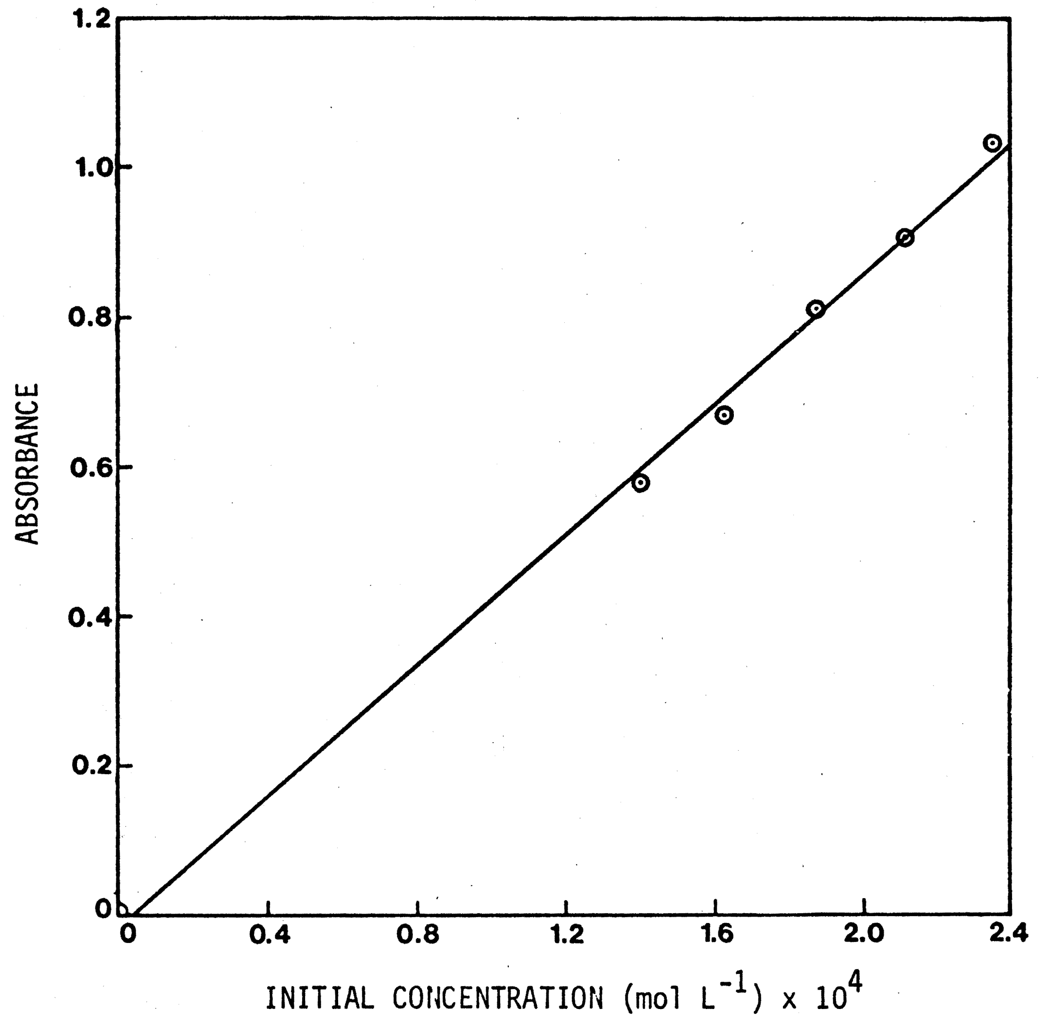
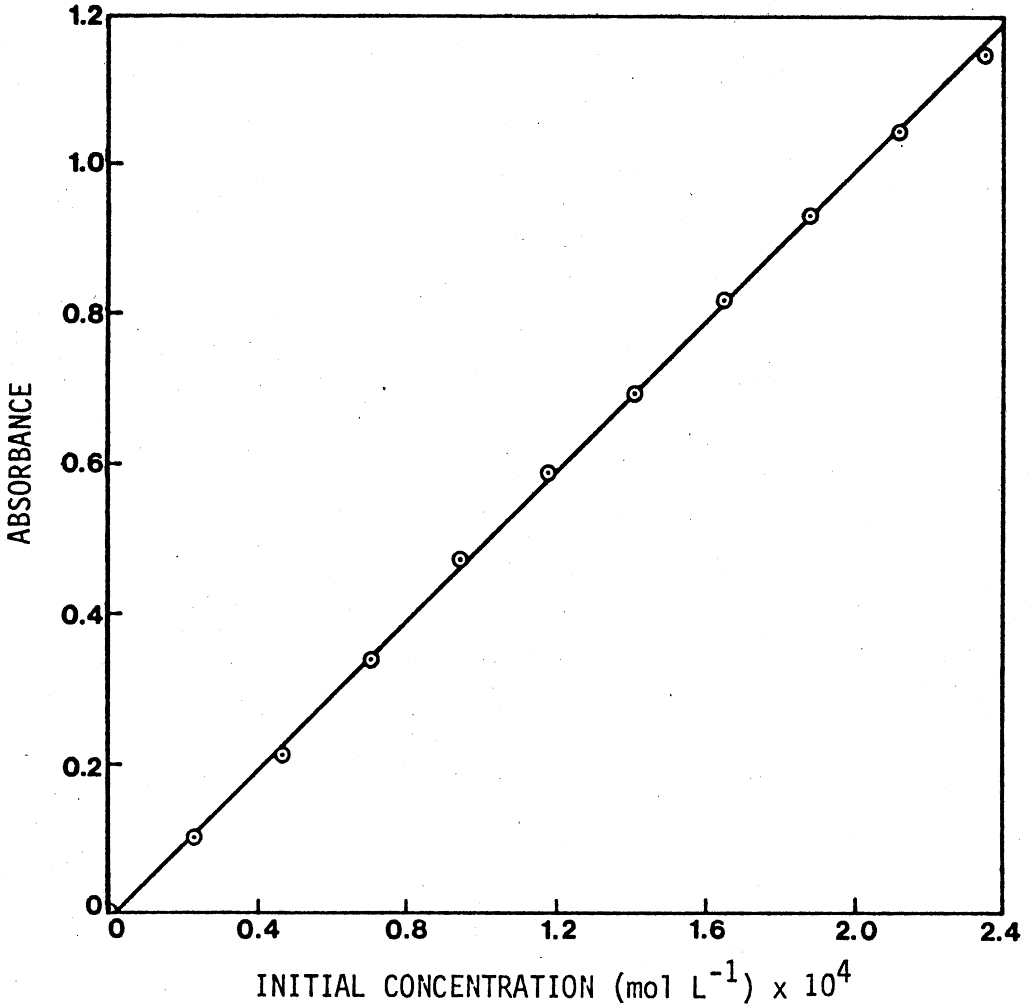

1.2
1.0
0.8
0.6
0.4
0.2
0
ABSORBANCE
0
0.4
0.8
1.2
1.6
2.0
2.4
INITIAL CONCENTRATION (mol L^{-1}) x 10^4

Figure 13. Verification of Beer-Lambert Law, Plot of Initial Concentration (t_o + 30 min) of Ester $\underset{\sim}{\underline{1a}}$ in 0.265 mM Hydrochloric Acid (pH = 3.6) Versus Absorbance at λ = 268 nm and T = 25 ± 0.1°C.


ABSORBANCE
1.2
1.0
0.8
0.6
0.4
0.2
0
0
0.4
0.8
1.2
1.6
2.0
2.4
INITIAL CONCENTRATION (mol L^{-1}) x 10^4

easily seen from Figure 13. For a pseudo first-order reaction, the extent of the reaction is independent of the initial concentration. Consequently, every solution used in the above experiment would have undergone the same fraction of the reaction during the initial period of 30 min (i.e. from the time 1a was dissolved to the time at which the absorbance readings were recorded). The frection f of the reaction for a pseudo first-order case is given by Eq. (51):

$$\ln \frac{1}{(1-f)} = k_{obs}\, t \tag{51}$$

Substituting the value of k_{obs} for the hydrolysis of 1a in 0.265 mM HCl at 25°C from Table III, we find $k_{obs} = 4.31 \times 10^{-5}\ \text{sec}^{-1}$, and t = 30 min = 30 x 60 sec. From Eq. (51), solving for f gives:

$$f = 0.075 \text{ (or 7.5\%)} \tag{52}$$

Thus, if f denotes the fraction of the reaction in 30 min, then from mass balance[a] one could write Eq. (53) for the observed absorbance $(A)_f$ (ℓ is not explicitly included in the equation since ℓ = 1 cm in all the experiments).

---

[a] There is evidence from ^{31}P NMR analysis that the keto form in ester 1a is instantaneously converted into an equilibrium mixture of two hydrated forms postulated as 39a and 49a. Hydrates 39a and 40a exist in an equilibrium with vanishingly small amounts of 1a (Scheme V). Stoichiometric amounts of 27a would result from the absorbing species (a mixture of 39a and 40a) in the steady state (Figure 2). The species in solution responsible for absorbance is assumed to be the hydrated form 39a, and the apparent molar absorptivity $(\varepsilon)_{t\to o}$ measured in aqueous acid solutions of 1a would be given by $(\varepsilon_{39a}/1 + K'_{eq})$ where K'_{eq} is the equilibrium constant for the equilibrium $39a \overset{K'_{eq}}{\rightleftharpoons} 40a$ (see Discussion section Eqs. (39) and (41), p. 90).

$$(A)_f = (\varepsilon)_{t\to o}\,(C_{\underset{\sim}{1a}})_o\,(1-f) + \varepsilon_2 (C_{\underset{\sim}{27a}})_f \tag{53}$$

and

$$(C_{\underset{\sim}{27a}})_f = (C_{\underset{\sim}{1a}})_o\, f \tag{54}$$

$(A)_f$ = experimentally measured absorbance at fraction f of the reaction

$(\varepsilon)_{t\to o}$ = apparent molar absorptivity for ester $\underset{\sim}{1a}$ in the corresponding solution extrapolated to $t\to o$

ε_2 = molar absorptivity of $\underset{\sim}{27a}$

$(C_{\underset{\sim}{1a}})_o$ = initial molar concentration of ester $\underset{\sim}{1a}$

$(C_{\underset{\sim}{27a}})_f$ = molar concentration of $\underset{\sim}{27a}$ at fraction of the reaction f and

f = fraction of the reaction.

Combining Eqs. (53) and (54), we have Eq. (55):

$$(A)_f = (\varepsilon)_{t\to o}(C_{\underset{\sim}{1a}})_o\,(1-f) + \varepsilon_2 (C_{\underset{\sim}{1a}})_o\, f \tag{55}$$

Equation (55) can be rewritten to give Eq. (56) which would predict

$$(A)_f = \left((\varepsilon)_{t\to o}\,(1-f) + \varepsilon_2 f\right)(C_{\underset{\sim}{1a}})_o \tag{56}$$

a linearity of the function $(A)_f$ plotted against $(C_{\underset{\sim}{1a}})_o$ with a slope = $\left((\varepsilon_1)_{t\to o}\,(1-f) + \varepsilon_2 f\right)$ and passing through the origin. The least squares parameters evaluated from the experimental values of $(A)_f$ and $(C_{\underset{\sim}{1a}})_o$ were found to be:

Slope = $\left((\varepsilon_1)_{t\to o}(1-f) + \varepsilon_2 f\right)$ = 4955 M^{-1} cm^{-1} intercept = -0.008, and R^2 = 0.999.

For the above case when t = 30 min, and

$$k_{obs} = 4.31 \times 10^{-5}\ sec^{-1};$$

from Eq. (52), f = 0.075. Using these values of f = 0.075 and ε_2 = 815 M^{-1} cm^{-1}, from (Table II), $(\varepsilon_{1a})_{t\to o}$ was calculated from the least squares slope and was found to be $(\varepsilon_1)_{t\to o}$ = 5290 M^{-1} cm^{-1}. This value is in reasonably close agreement within 2.5% with value of ε_1 = 5425 ± 25 M^{-1} cm^{-1} obtained from extrapolation of initial rates for solutions of 1a in 0.265 mM HCl by the method described earlier. Values of ε_1 for solutions of 1a in hydrochloric acid solutions of various concentrations evaluated from initial rates are summarized in Table II (see page 28).

Procedure for Kinetic Studies on the Hydrolysis of Ester 1a in Water and in Aqueous Hydrochloric Acid Solutions

The concentration range used for ester 1a was 0.2-0.3 mM. A sample of ester 1a (5 μL) was withdrawn with a micro syringe from a vial and was placed in a previously weighed parafilm boat which was then weighed on a microbalance. This sample was dissolved (over a period of 60 sec) in 100 mL of distilled water or in standard hydrochloric acid solutions, which were kept in a previously thermostated, stoppered Erlenmeyer flask. The temperature of the bath was maintained within ± 0.1°C of the specified temperature by using a Magniwhirl constant temperature system. The temperature of the UV cell was maintained by using a water circulating pump with bath reservoir held at constant temperature [reported temperature ± 0.1°C (Table V)]. Measurement of the absorbance of the reaction mixture was made at the wavelength (λ = 268 nm) corresponding to the $\pi \rightarrow \pi^*$ transition. Absorbance readings were recorded on a Cary Model-14 recording spectrophotometer. The time taken for recording the absorbance for each reading was 10-30 sec. Aliquots of the reaction mixture were withdrawn at specified time intervals and were placed in a 1 cm quartz UV cell, and solvent alone was added to an identical reference cell. Base-line reading was adjusted at ~0.050 with solvent in both the cells. In aqueous solutions at high temperature (35°C), absorbance readings were continuously monitored for the initial period (*ca.* 5-10 min) of the reaction followed by assessment of the absorbance up to 90% of reaction (20-30 readings). Also, analysis was made for any decomposition of **1a** in an aqueous solution by UV radiation[93] at = 268 nm and was found to be negligible as judged by comparison of absorbance readings obtained by continuous monitoring of this solution with those for aliquots removed over the initial period of exposure.

In order to measure the variation of pH during the reaction, the pH of the reaction mixture was separately monitored with solutions of **1a** identical in concentration with those used for kinetic studies. Acidity (pH) was monitored at regular intervals of time up to about 4 half lives. The variation in pH for solutions of **1a** in hydrochloric acid was found to be only ± 0.03 over a period of 4 half lives.

Fresh samples of D_2O were used for each *run* while monitoring the absorbance of **1a** in D_2O to estimate the solvent isotopic effect. The apparent initial absorbance of **1a** was found to fall by 20% when older samples of D_2O were used and such samples of D_2O were found to contain HOD as detected by ^1H NMR analysis.

Calculation of Rate Constants

Rate constants were calculated for a pseudo first-order reaction from Eqs. (41) and (42) (derived in the Discussion section, page 90), using a least squares procedure.

$$- \log_e (C)_t = - \log_e (C)_o + k_{obs}\, t \tag{41}$$

and

$$(C)_t = \frac{(A_T)_t - \varepsilon_2 (C_{\underset{\sim}{1a}})_o}{\varepsilon_1 - \varepsilon_2} \tag{42}$$

where $(C)_t$ = combined molar concentration of the substrate species at any instant of time t, i.e., $(C)_t = (C_{\underset{\sim}{39a}} + C_{\underset{\sim}{40a}})_t$. Thus $(C)_o$ = combined molar concentration of the substrate species as $t \to o$, i.e., $(C)_o = (C_{\underset{\sim}{39a}} + C_{\underset{\sim}{40a}})_{t \to o}$ is assumed to be $(C_{\underset{\sim}{1a}})_o$ and k_{obs} is the observed pseudo first-order rate constant defined by Eqs. (22) and (24) at a given temperature [see page 86 for Eqs. (22) and (24)]. Consequently $(A_T)_t$ = experimental absorbance measured for a solution of $\underset{\sim}{1a}$ at time t and $\varepsilon_1 \equiv (\varepsilon_{\underset{\sim}{1a}})_{t \to o} \equiv (\varepsilon_{\underset{\sim}{39a}}/1 + K'_{eq})$ is the apparent molar absorptivity of species existing in solution of $\underset{\sim}{1a}$ [see Eq. (39), page 90] and ε_2 = molar absorptivity of $\underset{\sim}{27a}$.

Recalling Eq. (38), one could write:

$$(A_T)_t = \varepsilon_1 (C)_t + \varepsilon_2 \Big((C_{\underset{\sim}{1a}})_o - (C)_t \Big) \tag{57}$$

Also note that

$$(A_S)_t = \varepsilon_1 (C)_t \tag{58}$$

and

$$(A_S)_t = (A_T)_t - \varepsilon_2(C_{\underset{\sim}{1a}})_o + \varepsilon_2(C)_t \qquad (59)$$

where $(A_S)_t$ = absorbance of the substrate species alone at time t.

The least squares slopes (k_{obs}) were evaluated from Eqs. (41) and (42) using the experimental values of $(A_T)_t$ measured at various intervals of time t. The values of ε_1 and ε_2 evaluated experimentally, as explained previously and used for the calculations of k_{obs}, are summarized in Table II, page 28. Calculations were programmed on the University IBM 70 computer. The computer program also included an iterative procedure described below for the evaluation of ε_1 starting with the experimentally determined value (as described previously) as the first value.

For a given value of ε_1, a set of $(C)_t$ values corresponding to a set of $(A_T)_t$ values were generated from Eq. (42). These values of $(C)_t$ were inserted into Eq. (59), which would in turn generate a set of $(A_S)_t$ values corresponding to the set of $(C)_t$ values generated in the previous step. Now, a least squares procedure was adopted to extract ε_1 from Eq. (58) using the sets of $(A_S)_t$ values and the corresponding $(C)_t$ values evaluated as explained previously. Interestingly the iterated values of ε_1 were found to differ from the initial value of ε_1 (experimentally evaluated) only in the 6th significant figure.

Evaluation of Rate Constants for Hydrolysis of Ester **1a** in Hydrochloric Acid Solutions at Various pH Values (Runs 1-8)

The Rate of Hydrolysis of Ester **1a** in 10.0 mM Hydrochloric Acid at 30°C; Run 1

Exactly 100 mL of 10.0 mM standard hydrochloric acid was thermostated in a stoppered Erlenmeyer flask. A 5 μL sample of ester **1a** was withdrawn into a weighed parafilm boat and was weighed again accurately in a microbalance. The weight of the sample was 5.70 mg. The weighed sample along with the parafilm boat was carefully dropped into the previously thermostated Erlenmeyer flask containing measured volume of standard hydrochloric acid. The flask was shaken thoroughly to dissolve the ester **1a** completely over a period of 30-60 sec and was left in the constant temperature bath. Aliquots of *ca.* 2 mL were withdrawn and absorbance readings were recorded as described earlier. The time required for the transfer of the aliquot from the reaction flask to the cell compartment (maintained at bath temperature by water circulation) was in every case 20-30 sec. A typical set of experimental data is summarized in Table XII along with the calculated least squares parameters. Experiments were performed in duplicate (standard deviation in $k_{obs} < 2\%$).

The Rate of Hydrolysis of Ester **1a** in 5.00 mM Hydrochloric Acid at 30°C; Run 2

The experiment was repeated exactly as described in Run 1 except that the solvent taken in the Erlenmeyer flask was 100 mL of 5.00 mM

TABLE XII

THE RATE OF HYDROLYSIS OF ESTER **1a** IN 10.0 mM HYDROCHLORIC ACID AT 30°C; RUN 1*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\text{Log}_e\ (C)_t$
3.0	1.318	0.052	1.266	1.267	0.2366	8.3490
59.0	1.310	0.052	1.258	1.258	0.2348	8.3566
215.0	1.270	0.048	1.222	1.215	0.2268	8.3915
420.0	1.200	0.047	1.153	1.132	0.2114	8.4619
725.0	1.108	0.020	1.088	1.054	0.1969	8.5331
1350.0	1.030	0.050	0.980	0.925	0.1727	8.6639
1760.0	0.940	0.055	0.885	0.811	0.1515	8.7950
2185.0	0.880	0.060	0.820	0.733	0.1370	8.8958
2700.0	0.810	0.050	0.760	0.662	0.1236	8.9988
3157.0	0.750	0.052	0.698	0.587	0.1097	9.1178
3613.0	0.706	0.053	0.653	0.534	0.0996	9.2139
4130.0	0.652	0.054	0.598	0.468	0.0874	9.3456
4575.0	0.615	0.055	0.560	0.422	0.0789	9.4478
5065.0	0.578	0.053	0.525	0.380	0.0710	9.5523
5590.0	0.544	0.055	0.489	0.337	0.0630	9.6725
6120.0	0.523	0.055	0.468	0.312	0.0583	9.7499
6570.0	0.490	0.053	0.437	0.275	0.0514	9.8764
7350.0	0.463	0.055	0.408	0.240	0.0449	10.0112

TABLE XII (Continued)

$*(A_T)_t = A_E - A_{sol}$

Weight of ester $\underset{\sim}{1a}$ dissolved in 100 mL of 10.0 mM hydrochloric acid = 5.70 mg.

Temp = 30 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 5355\ M^{-1}\ cm^{-1}$; $\varepsilon_2 = 880\ M^{-1}\ cm^{-1}$; $(pH)_{average} = 2.04 \pm 0.03$;

Number of data points = 18

Experiment #1

$(C_{\underset{\sim}{1a}})_o = 0.2353$ mM; $\left((C_{\underset{\sim}{1a}})_o\right)_{calc} = 0.2324$ mM; $k_{obs} = 3.84 \times 10^{-6}\ sec^{-1}$; $R^2 = 0.998$

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.2353$ mM; $\left((C_{\underset{\sim}{1a}})_o\right)_{calc} = 0.2271$ mM; $k_{obs} = 3.76 \times 10^{-6}\ sec^{-1}$; $R^2 = 0.996$

$k_{obs}(average) = (3.80 \pm 0.06) \times 10^{-6}\ sec^{-1}$

hydrochloric acid. The temperature was maintained at 30°C. The results are tabulated in Table XIII. The experiment was performed in duplicate. The above two runs 1 and 2 were performed for the hydrolysis of ester **1a** in 10.0 mM and 5.0 mM hydrochloric acid, respectively, at the higher temperature (30°C), since the rate of decay of absorbance was found to be much slower in strong acid solutions. The subsequent runs in less concentrated hydrochloric acid described below were performed at 25°C.

The Rate of Hydrolysis of Ester 1a in 1.06 mM Hydrochloric Acid at 25°C; Run 3

The experiment was repeated exactly as described earlier with 100 mL of 1.06 mM hydrochloric acid as the solvent. The temperature was maintained at 25°C. Results are summarized in Table XIV. The experiment was performed in duplicate.

The Rate of Hydrolysis of Ester 1a in 0.795 mM Hydrochloric Acid at 25°C; Run 4

The experiment was repeated exactly as described earlier with 100 mL of 0.795 mM hydrochloric acid as the solvent. Results are summarized in Table XV. The experiment was performed in duplicate.

The Rate of Hydrolysis of Ester 1a in 0.530 mM Hydrochloric Acid at 25°C; Run 5

The experiment was repeated exactly as described earlier with 100 mL of 0.530 mM hydrochloric acid as the solvent and bath temperature at 25°C. Results are summarized in Table XVI. The experiment was performed in duplicate.

TABLE XIII

THE RATE OF HYDROLYSIS OF ESTER **1a** IN 5.0 mM HYDROCHLORIC ACID AT 30°C; RUN 2*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-Log_e\ (C)_t$
5.0	1.295	0.050	1.245	1.244	0.2326	8.3662
81.0	1.268	0.055	1.213	1.206	0.2255	8.3972
212.0	1.210	0.055	1.155	1.376	0.2126	8.4559
345.0	1.175	0.050	1.125	1.102	0.2060	8.4877
468.0	1.130	0.055	1.075	1.043	0.1949	8.5431
568.0	1.105	0.055	1.050	1.013	0.1894	8.5719
770.0	1.070	0.060	1.010	0.966	0.1805	8.6199
1315.0	0.880	0.048	0.832	0.754	0.1410	8.8669
1500.0	0.865	0.055	0.810	0.728	0.1361	8.9021
1740.0	0.810	0.050	0.760	0.669	0.1250	8.9871
1863.0	0.780	0.054	0.726	0.628	0.1175	9.0493
2073.0	0.746	0.050	0.696	0.593	0.1108	9.1076
2195.0	0.726	0.050	0.676	0.569	0.1064	9.1485
2715.0	0.642	0.054	0.588	0.465	0.0869	9.3512
2895.0	0.621	0.055	0.566	0.439	0.0820	9.4090
3155.0	0.585	0.057	0.528	0.394	0.0736	9.5175
3352.0	0.565	0.055	0.510	0.372	0.0696	9.5733
3645.0	0.537	0.053	0.484	0.341	0.0638	9.6599
4175.0	0.495	0.055	0.440	0.289	0.0540	9.8259
4595.0	0.463	0.058	0.405	0.248	0.0463	9.9810
5145.0	0.424	0.053	0.371	0.207	0.0387	10.1590

TABLE XIII (Continued)

*$(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 5.0 mM hydrochloric acid = 5.65 mg.

Temp = 30 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 5350\ M^{-1}\ cm^{-1}$; $\varepsilon_2 = 840\ M^{-1}\ cm^{-1}$; $(pH)_{average} = 2.33 \pm 0.3$;

Number of data points = 21

Experiment #1

$(C_{\mathbf{1a}})_o = 0.2333$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2300$ mM; $k_{obs} = 0.586 \times 10^{-5}\ sec^{-1}$; $R^2 = 0.999$

Experiment #2

$(C_{\mathbf{1a}})_o = 0.2353$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2294$ mM; $k_{obs} = 0.577 \times 10^{-5}\ sec^{-1}$; $R^2 = 0.998$

k_{obs}(average) = $(0.582 \pm 0.006) \times 10^{-5}\ sec^{-1}$

TABLE XIV

THE RATE OF HYDROLYSIS OF ESTER **1a** IN 1.06 mM HYDROCHLORIC ACID AT 25°C; RUN 3*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-Log_e\ (C)_t$
5.0	1.315	0.050	1.265	1.263	0.2334	8.3626
16.0	1.295	0.050	1.245	1.240	0.2290	8.3816
85.0	1.270	0.050	1.220	1.210	0.2236	8.4059
135.0	1.235	0.050	1.185	1.168	0.2159	8.4409
200.0	1.200	0.050	1.150	1.267	0.2082	8.4771
270.0	1.155	0.050	1.105	1.073	0.1983	8.5258
335.0	1.100	0.050	1.050	1.008	0.1862	8.5887
390.0	1.075	0.050	1.025	0.978	0.1807	8.6186
465.0	1.050	0.050	1.000	0.948	0.1752	8.6495
610.0	0.980	0.050	0.930	0.865	0.1598	8.7413
730.0	0.910	0.050	0.860	0.782	0.1445	8.8425
1100.0	0.742	0.050	0.692	0.582	0.1076	9.1375
1310.0	0.670	0.050	0.620	0.496	0.0917	9.2965
1615.0	0.572	0.050	0.522	0.380	0.0702	9.5640
1885.0	0.525	0.050	0.475	0.324	0.0599	9.7230
2290.0	0.462	0.050	0.412	0.249	0.0461	9.9859
2550.0	0.436	0.050	0.386	0.218	0.0403	10.1183
3025.0	0.380	0.050	0.330	0.152	0.0280	10.4821
3345.0	0.350	0.050	0.302	0.118	0.0219	10.7299
3600.0	0.340	0.050	0.290	0.104	0.0193	10.8582

TABLE XIV (Continued)

$*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 1.06 mM hydrochloric acid = 5.70 mg.

Temp = 25 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 5410\ M^{-1}cm^{-1}$; $\varepsilon_2 = 860\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.0 \pm 0.03$;

Number of data points = 20

Experiment #1

$(C_{\mathbf{1a}})_o = 0.2353$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2368$ mM; $k_{obs} = 1.18 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

Experiment #2

$(C_{\mathbf{1a}})_o = 0.2353$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2339$ mM; $k_{obs} = 1.19 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

$k_{obs}(average) = (1.185 \pm 0.007) \times 10^{-5} sec^{-1}$

TABLE XV

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.795 mM HYDROCHLORIC ACID AT 25°C; RUN 4*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-Log_e$ $(C)_t$
4.0	1.320	0.050	1.270	1.269	0.2307	8.3746
28.0	1.310	0.050	1.262	1.260	0.2289	8.3821
44.0	1.290	0.050	1.240	1.234	0.2242	8.4031
81.0	1.232	0.050	1.182	1.165	0.2116	8.4606
121.0	1.202	0.050	1.152	1.129	0.2052	8.4917
180.0	1.150	0.050	1.100	1.067	0.1939	8.5481
252.0	1.110	0.050	1.060	1.020	0.1853	8.5936
324.0	1.072	0.050	1.022	0.975	0.1771	8.6390
410.0	0.980	0.050	0.930	0.865	0.1572	8.7580
520.0	0.914	0.050	0.864	0.787	0.1429	8.8531
610.0	0.868	0.050	0.818	0.732	0.1330	8.9252
700.0	0.810	0.050	0.760	0.663	0.1205	9.0241
825.0	0.740	0.050	0.690	0.580	0.1053	9.1583
1290.0	0.572	0.050	0.522	0.380	0.0691	9.5807
1550.0	0.498	0.050	0.448	0.292	0.0531	9.8441
1910.0	0.423	0.050	0.373	0.203	0.0369	10.2085
2175.0	0.388	0.050	0.338	0.161	0.0293	10.4381
3007.0	0.320	0.050	0.270	0.080	0.0146	11.1342

TABLE XV (Continued)

$^*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 0.795 mM hydrochloric acid = 5.60 mg.

Temp = 25 ± 0.1°C; λ = 268 nm; ε_1 = 5500 $M^{-1}cm^{-1}$; ε_2 = 875 $M^{-1}cm^{-1}$; $(pH)_{average}$ = 3.13 ± 0.03;

Number of data points = 18

Experiment #1

$(C_{\mathbf{1a}})_o$ = 0.2312 mM; $\{(C_{\mathbf{1a}})_o\}_{calc}$ = 0.2318 mM; $k_{obs} = 1.56 \times 10^{-5} sec^{-1}$; R^2 = 0.999

Experiment #2

$(C_{\mathbf{1a}})_o$ = 0.2333 mM; $\{(C_{\mathbf{1a}})_o\}_{calc}$ = 0.2339 mM; $k_{obs} = 1.57 \times 10^{-5} sec^{-1}$; R^2 = 0.999

$k_{obs}(\text{average}) = (1.565 \pm 0.007) \times 10^{-5} sec^{-1}$

TABLE XVI

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.530 mM HYDROCHLORIC ACID AT 25°C; RUN 5*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\text{Log}_e\ (C)_t$
8.0	1.300	0.050	1.250	1.245	0.2252	8.3985
21.0	1.210	0.050	1.260	1.257	0.2274	8.3890
35.0	1.270	0.050	1.220	1.209	0.2188	8.4276
46.0	1.251	0.050	1.201	1.186	0.2147	8.4465
63.0	1.242	0.050	1.192	1.176	0.2127	8.4555
70.0	1.235	0.050	1.185	1.167	0.2112	8.4626
106.0	1.172	0.050	1.122	1.092	0.1977	8.5290
138.0	1.124	0.050	1.074	1.035	0.1873	8.5827
176.0	1.075	0.050	1.025	0.977	0.1768	8.6406
203.0	1.060	0.050	1.010	0.959	0.1736	8.6590
251.0	1.010	0.050	0.960	0.900	0.1628	8.7230
259.0	0.995	0.050	0.945	0.882	0.1596	8.7431
305.0	0.952	0.050	0.902	0.831	0.1503	8.8028
345.0	0.915	0.050	0.865	0.787	0.1424	8.8573
455.0	0.822	0.050	0.772	0.676	0.1223	9.0088
535.0	0.760	0.050	0.710	0.602	0.1090	9.1243
620.0	0.722	0.050	0.672	0.557	0.1008	9.2023
760.0	0.632	0.050	0.582	0.450	0.0814	9.4157
1215.0	0.455	0.050	0.405	0.240	0.0433	10.0463
1485.0	0.380	0.050	0.330	0.150	0.0272	10.5122
1845.0	0.332	0.050	0.282	0.093	0.0169	10.9899

TABLE XVI (Continued)

$^*(A_T)_t = A_E - A_{sol}$

Weight of ester 1a dissolved in 100 mL of 0.530 mM hydrochloric acid = 5.60 mg.

Temp = 25 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 5530\ M^{-1}cm^{-1}$; $\varepsilon_2 = 880\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.35 \pm 0.03$;

Number of data points = 21

Experiment #1

$(C_{1a})_o = 0.2312$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2314$ mM; $k_{obs} = 2.35 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

Experiment #2

$(C_{1a})_o = 0.2312$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2317$ mM; $k_{obs} = 2.39 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

k_{obs}(average) = $(2.37 \pm 0.01) \times 10^{-5} sec^{-1}$

The Rate of Hydrolysis of Ester **1a** in 0.265 mM Hydrochloric Acid at 25°C; Run 6

The experiment was repeated exactly as described earlier with 100 mL of 0.265 mM hydrochloric acid as the solvent and bath temperature at 25°C. Results are summarized in Table XVII. A duplicate run was performed.

The Rate of Hydrolysis of Ester **1a** in 0.106 mM Hydrochloric Acid at 25.7°C; Run 7

The experiment was repeated exactly as described earlier with solvent as 100 mL of 0.106 mM hydrochloric acid and bath temperature at 25.7°C. Results are summarized in Table XVIII. A duplicate run was performed.

The Rates of Hydrolysis of Ester **1a** in 0.50 mM Hydrochloric Acid at 25°C with Varying Initial Concentration of the Substrate; Run 8

In order to ascertain whether the observed rate of hydrolysis was governed by a pseudo first-order behavior, rates of hydrolysis were measured exactly as described earlier with 100 mL of 0.50 mM hydrochloric acid as the solvent. In Experiment 1, 4.6 mg (4 μL) of ester **1a** was used and, in Experiment 2, 6.85 mg (6 μL) of ester **1a** was dissolved in 100 mL of solvent. Each experiment was performed in duplicate and the results are summarized in Table XIX. It is clear from data on Table XIX that the rate constant k_{obs} is independent of the initial concentration of **1a**, as would be expected for a pseudo first-order reaction.

TABLE XVII

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.265 mM HYDROCHLORIC ACID AT 25°C; RUN 6*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e\ (C)_t$
6.0	1.310	0.050	1.260	1.257	0.2318	8.3696
16.0	1.275	0.050	1.225	1.216	0.2242	8.4029
32.0	1.225	0.050	1.175	1.571	0.2134	8.4525
42.0	1.200	0.050	1.150	1.128	0.2079	8.4783
60.0	1.148	0.050	1.098	1.066	0.1967	8.5341
75.0	1.110	0.050	1.060	1.022	0.1884	8.5769
102.0	1.040	0.050	0.990	0.939	0.1732	8.6610
135.0	0.985	0.050	0.935	0.875	0.1613	8.7324
170.0	0.905	0.050	0.855	0.780	0.1439	8.8463
200.0	0.862	0.050	0.812	0.730	0.1346	8.9134
230.0	0.815	0.050	0.765	0.675	0.1244	8.9922
262.0	0.760	0.050	0.710	0.610	0.1124	9.0931
300.0	0.712	0.050	0.662	0.553	0.1020	9.1903
350.0	0.659	0.050	0.609	0.491	0.0905	9.3100
402.0	0.617	0.050	0.567	0.441	0.0814	9.4161
460.0	0.552	0.050	0.502	0.365	0.0673	9.6064
530.0	0.525	0.050	0.475	0.333	0.0614	9.6975
615.0	0.460	0.050	0.410	0.257	0.0473	9.9584
765.0	0.390	0.050	0.340	0.174	0.0321	10.3456
1210.0	0.290	0.050	0.240	0.057	0.0104	11.4708

TABLE XVII (Continued)

$^*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of hydrochloric acid = 5.70 mg.

Temp = 25 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 5425\ M^{-1}cm^{-1}$; $\varepsilon_2 = 815\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.60 \pm 0.03$;

Number of data points = 20

Experiment #1

$(C_{\mathbf{1a}})_o = 0.2353$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2274$ mM; $k_{obs} = 4.27 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

Experiment #2

$(C_{\mathbf{1a}})_o = 0.2353$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2170$ mM; $k_{obs} = 4.35 \times 10^{-5} sec^{-1}$; $R^2 = 0.993$

$k_{obs}(average) = (4.31 \pm 0.06) \times 10^{-5} sec^{-1}$

TABLE XVIII

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.106 mM HYDROCHLORIC ACID AT 25.7°C; RUN 7*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\text{Log}_e\ (C)_t$
5.0	1.198	0.050	1.148	1.136	0.2169	8.4362
8.0	1.160	0.050	1.110	1.091	0.2083	8.4766
10.0	1.142	0.050	1.092	1.070	0.2042	8.4963
15.0	1.100	0.050	1.050	1.020	0.1947	8.5438
20.0	1.080	0.050	1.030	0.997	0.1902	8.5673
25.0	1.050	0.050	1.000	0.961	0.1835	8.6036
31.0	1.005	0.050	0.955	0.908	0.1733	8.6605
34.0	0.980	0.050	0.930	0.879	0.1677	8.6936
38.5	0.953	0.050	0.903	0.847	0.1616	8.7306
43.0	0.930	0.050	0.880	0.819	0.1564	8.7633
49.5	0.895	0.050	0.845	0.778	0.1485	8.8151
55.0	0.865	0.050	0.815	0.742	0.1417	8.8618
60.0	0.842	0.050	0.792	0.715	0.1365	8.8992
66.0	0.825	0.050	0.775	0.695	0.1327	8.9277
73.0	0.790	0.050	0.740	0.654	0.1248	8.9891
80.0	0.760	0.050	0.710	0.618	0.1180	9.0449
88.0	0.730	0.050	0.680	0.583	0.1112	9.1040
97.0	0.700	0.050	0.650	0.547	0.1044	9.1668
106.0	0.676	0.050	0.626	0.519	0.0990	9.2201
117.0	0.642	0.050	0.592	0.479	0.0914	9.3007
129.0	0.608	0.050	0.558	0.439	0.0837	9.3885

TABLE XVIII (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-Log_e\ (C)_t$
142.0	0.578	0.050	0.528	0.403	0.0769	9.4729
155.0	0.558	0.050	0.508	0.379	0.0724	9.5334
176.0	0.515	0.050	0.465	0.329	0.0627	9.6773
192.0	0.486	0.050	0.436	0.294	0.0561	9.7876
208.0	0.461	0.050	0.411	0.265	0.0505	9.8935
285.0	0.374	0.050	0.324	0.162	0.0309	10.3860
360.0	0.320	0.050	0.270	0.098	0.0187	10.8885

$^*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 0.106 mM hydrochloric acid = 5.65 mg.

Temp = 25.7 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 5240\ M^{-1}cm^{-1}$; $\varepsilon_2 = 810\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.94 \pm 0.03$;

Number of data points = 28

Experiment #1

$(C_{\mathbf{1a}})_o = 0.2312$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2110$ mM; $k_{obs} = 11.46 \times 10^{-5} sec^{-1}$; $R^2 = 0.997$

TABLE XVIII (Continued)

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.2353$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.2204$ mM; $k_{obs} = 11.78 \times 10^{-5} sec^{-1}$; $R^2 = 0.993$

k_{obs}(average) = $(11.62 \pm 0.23) \times 10^{-5} sec^{-1}$

TABLE XIX

THE RATES OF HYDROLYSIS OF ESTER **1a** IN 0.50 mM HYDROCHLORIC ACID AT 25°C WITH VARYING INITIAL CONCENTRATION OF SUBSTRATE; RUN 8*

Experiment	Weight of **1a** in 100mL Solvent (mg)	Initial Concentration of **1a** $(C_{\mathbf{1a}})_o$ (mM)	$\left[(C_{\mathbf{1a}})_o\right]_{calc}$ (mM)	$k_{obs} \times 10^5$ sec^{-1}	R^2
1	46.0	0.1899	0.1761	2.72	0.997
Duplicate 1	45.0	0.1858	0.1781	2.67	0.998
2	68.5	0.2828	0.2683	2.67	0.999
Duplicate 2	70.0	0.2890	0.2705	2.66	0.999

*Temp = 25 ± 0.1°C; $\lambda = 268$ nm;

$\varepsilon_1 = 5500\ M^{-1}cm^{-1}$; $\varepsilon_2 = 875\ M^{-1}cm^{-1}$;

$(pH)_{average} = 3.28 \pm 0.03$; Number of data points = 19-21

Investigation of Other Reaction Orders for Hydrolysis of Ester 1a in Hydrochloric Acid

Concentration functions corresponding to the zero, first, second and third order rate laws were evaluated from data presented in Table XV for run 4 as a test case. The corresponding functions are summarized in Table XX. The least squares correlation coefficient R^2 for zero, first, second and third order fit were found to be: $R^2 = 0.87$ (0), 0.999 (1), 0.894 (2), and 0.65 (3), respectively. The corresponding plots of the concentration functions can be seen in Figure 5. It is clear that only the pseudo first-order function $[\phi_1 = -\log_e(C)_t]$ is linear with time which supports the assumption that the observed reaction is pseudo first-order. Pseudo first-order plots for hydrolysis of ester 1a in other hydrochloric acid solutions can be seen in Figure 4.

The Rate of Hydrolysis of Ester 1a in Water in the Absence of Hydrochloric Acid at 25°C; Run 9

In order to determine if the hydrolysis of ester 1a was catalyzed by externally added hydrochloric acid, the rates were measured for hydrolysis of 1a in distilled water in the absence of any external acid. The experiment was performed exactly as described previously with 100 mL of distilled water as the solvent. Results are tabulated in Table XXI. Six more runs were performed. The pH of a solution of 1a at the above concentration was monitored separately for over 4 half lives. The pseudo first-order plot along with the variation of pH could be seen in Figure 3 for an aqueous solution of ester 1a (0.2353 mM) in water.

TABLE XX

INVESTIGATION OF OTHER REACTION ORDERS* FOR HYDROLYSIS OF ESTER 1a IN HYDROCHLORIC ACID: FROM DATA ON TABLE XV

	Time (t) (min)	Concentration of substrate (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e (C)_t$	$1/(C)_t$ $(mM)^{-1}$	$1/(C)_t^2$ $(mM)^{-2}$
	4.0	0.2306	8.3746	4.336	18.81
	28.0	0.2289	8.3821	4.369	19.09
	44.0	0.2242	8.4031	4.460	19.90
	81.0	0.2116	8.4606	4.726	22.33
	121.0	0.2052	8.4917	4.873	23.75
	180.0	0.1939	8.5481	5.157	26.60
	252.0	0.1853	8.5936	5.397	29.12
	324.0	0.1771	8.6390	5.647	31.88
	410.0	0.1572	8.7580	6.361	40.47
	520.0	0.1429	8.8531	6.998	48.98
	610.0	0.1330	8.9252	7.519	56.53
	700.0	0.1205	9.0241	8.299	68.87
	825.0	0.1053	9.1583	9.497	90.19
	1290.0	0.0691	9.5807	14.470	209.40
	1550.0	0.0531	9.8441	18.830	354.70
	1910.0	0.0369	10.2085	27.100	734.40
	2175.0	0.0293	10.4381	34.130	1165.00
	3007.0	0.0146	11.1342	68.490	4691.00
Least Squares Correlation Coefficient:	R^2 =	0.87	0.999	0.894	0.65

*See Figure 5 for plots of the different concentration functions vs time for zero, first, second and third-order reactions.

TABLE XXI

THE RATE OF HYDROLYSIS OF ESTER 1a IN WATER IN THE ABSENCE OF HYDROCHLORIC ACID AT 25°C; RUN 9*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e\ (C)_t$
4.0	0.923	0.048	0.875	0.842	0.1935	8.5503
4.5	0.892	0.048	0.844	0.804	0.1848	8.5965
5.0	0.870	0.048	0.822	0.777	0.1786	8.6306
5.5	0.852	0.048	0.804	0.755	0.1735	8.6594
6.0	0.838	0.048	0.790	0.738	0.1696	8.6823
7.0	0.810	0.048	0.762	0.703	0.1617	8.7299
8.0	0.782	0.048	0.734	0.669	0.1538	8.7799
9.0	0.750	0.048	0.702	0.630	0.1448	8.8402
10.5	0.732	0.048	0.684	0.608	0.1397	8.8759
11.0	0.726	0.048	0.678	0.600	0.1380	8.8880
11.5	0.718	0.048	0.670	0.591	0.1358	8.9045
12.0	0.715	0.048	0.667	0.587	0.1349	8.9107
13.0	0.692	0.048	0.644	0.559	0.1285	8.9599
14.5	0.675	0.048	0.627	0.538	0.1237	8.9978
15.5	0.665	0.048	0.617	0.526	0.1209	9.0208
16.5	0.658	0.048	0.610	0.517	0.1189	9.0373
18.0	0.640	0.048	0.592	0.495	0.1138	9.0808
19.0	0.632	0.048	0.584	0.485	0.1116	9.1008
20.0	0.620	0.048	0.572	0.471	0.1082	9.1315
21.0	0.616	0.048	0.568	0.466	0.1071	9.1420
22.0	0.596	0.048	0.548	0.441	0.1014	9.1960

TABLE XXI (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e (C)_t$
24.0	0.570	0.048	0.522	0.409	0.0941	9.2709
26.0	0.562	0.048	0.514	0.400	0.0919	9.2951
28.0	0.556	0.048	0.508	0.392	0.0902	9.3136
30.0	0.550	0.048	0.502	0.385	0.0885	9.3325
23.0	0.542	0.048	0.494	0.375	0.0862	9.3583
34.0	0.530	0.048	0.482	0.360	0.0829	9.3983
36.0	0.520	0.048	0.472	0.348	0.0801	9.4328
38.0	0.512	0.048	0.464	0.338	0.0778	9.4613
40.0	0.500	0.048	0.452	0.324	0.0744	9.5057
42.0	0.490	0.048	0.442	0.312	0.0716	9.5443
44.0	0.482	0.048	0.434	0.302	0.0694	9.5762
47.0	0.470	0.048	0.422	0.287	0.0660	9.6261
50.0	0.454	0.048	0.406	0.267	0.0615	9.6968
54.0	0.432	0.048	0.384	0.240	0.0553	9.8030
58.0	0.420	0.048	0.372	0.226	0.0519	9.8660
62.0	0.410	0.048	0.360	0.214	0.0491	9.9218
68.0	0.395	0.048	0.347	0.195	0.0449	10.0117
72.0	0.378	0.048	0.330	0.174	0.0401	10.1244
78.0	0.370	0.048	0.322	0.165	0.0378	10.1823
84.0	0.354	0.048	0.306	0.145	0.0333	10.3090
90.0	0.340	0.048	0.292	0.128	0.0294	10.4348
96.0	0.325	0.048	0.277	0.109	0.0252	10.5898
104.0	0.318	0.048	0.270	0.101	0.0232	10.6713

TABLE XXI (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\mathrm{Log}_e\ (C)_t$
111.0	0.310	0.048	0.262	0.091	0.0210	10.7734
121.0	0.298	0.048	0.250	0.076	0.0176	10.9492

$*(A_T)_t = A_E - A_{sol}$

Weight of ester 1a dissolved in 100 mL of distilled water = 5.70 mg.

Temp = 25 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 4350\ M^{-1}cm^{-1}$; $\varepsilon_2 = 800\ M^{-1}cm^{-1}$; $(pH)_{average} = 4.4$

Number of data points = 47

Experiment #1

$(C_{1a})_o = 0.2353$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.1702$ mM; $k_{obs} = 32.8 \times 10^{-5} sec^{-1}$; $R^2 = 0.985$

Experiment #2

$(C_{1a})_o = 0.2353$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.1807$ mM; $k_{obs} = 31.4 \times 10^{-5} sec^{-1}$; $R^2 = 0.975$

TABLE XXI (Continued)

Experiment #3

$(C_{1a})_o = 0.2560$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2060$ mM; $k_{obs} = 28.7 \times 10^{-5}\,sec^{-1}$; $R^2 = 0.975$

Experiment #4

$(C_{1a})_o = 0.2642$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.1810$ mM; $k_{obs} = 36.9 \times 10^{-5}\,sec^{-1}$; $R^2 = 0.984$

Experiment #5

$(C_{1a})_o = 0.2457$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.1820$ mM; $k_{obs} = 32.2 \times 10^{-5}\,sec^{-1}$; $R^2 = 0.987$

Experiment #6

$(C_{1a})_o = 0.3468$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2879$ mM; $k_{obs} = 25.1 \times 10^{-5}\,sec^{-1}$; $R^2 = 0.972$

Experiment #7

$(C_{1a})_o = 0.3303$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2403$ mM; $k_{obs} = 21.6 \times 10^{-5}\,sec^{-1}$; $R^2 = 0.974$

k_{obs}(average) $= (32.4 \pm 3.0) \times 10^{-5}\,sec^{-1}$ (for runs 1 to 5 for the initial concentration range: 0.2353 mM - 0.2642 mM)

k_{obs}(average) $= (23.4 \pm 2.5) \times 10^{-5}\,sec^{-1}$ (for runs 5 and 6 for the initial concentration range: 0.3303 mM - 0.3468 mM)

Solvent Isotopic Effect: The Rate of Hydrolysis of Ester 1a in D_2O in the Absence of Hydrochloric Acid at 25°C; Run 10

The rate of hydrolysis of ester 1a in D_2O was monitored in order to evaluate the solvent isotopic effect. The experiments were repeated exactly as described earlier with 25-50 mL of D_2O as solvent and two different initial concentrations of ester 1a. Results are summarized in Table XXII. Values of pD for the solution of 1a in D_2O were assumed to be the same as the corresponding values of pH for a similar solution of ester 1a in H_2O. This was confirmed by measurement of the pH of a solution of ester 1a in D_2O (0.2395 mM) [Measured with a glass electrode which was standardized with buffer solutions in ordinary water]. The average value of the pH experimentally measured for the solution of ester 1a in D_2O was found to be 4.0 ± 0.05. The experimental value of pH measured as described above was converted into the corresponding pD values by using the correction factor reported by Covington and coworkers from the following equation.[28]

$$(pD)_{D_2O} = (pH)_{\text{measured in } D_2O} + 0.41$$

so that $(pD)_{\text{average}}$ for the solutions of ester 1a in D_2O used for the kinetic study was evaluated as $4.0 \pm 0.41 = 4.41 \pm 0.05$. The same values of ε_1 and ε_2 evaluated in aqueous solutions were used for the calculation of k_{D_2O}. The isotopic effect k_{H_2O}/k_{D_2O} evaluated from the corresponding values of k_{H_2O} is given in Table XXII.

TABLE XXII

RATE DATA IN D_2O AND SOLVENT ISOTOPIC EFFECT FOR THE HYDROLYSIS OF ESTER 1a AT 25°C; RUN 10*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-Log_e\ (C)_t$
3.0	0.978	0.045	0.933	0.917	0.2107	8.4649
3.5	0.950	0.045	0.905	0.882	0.2029	8.5031
4.0	0.920	0.045	0.875	0.846	0.1944	8.5456
4.5	0.898	0.045	0.853	0.819	0.1882	8.5779
5.0	0.880	0.045	0.835	0.797	0.1832	8.6052
5.5	0.878	0.045	0.833	0.794	0.1826	8.6083
6.0	0.866	0.045	0.821	0.780	0.1792	8.6270
7.0	0.842	0.045	0.797	0.750	0.1725	8.6654
8.0	0.830	0.045	0.785	0.735	0.1691	8.6852
9.0	0.822	0.045	0.777	0.726	0.1668	8.6986
10.0	0.792	0.045	0.747	0.689	0.1584	8.7505
12.0	0.768	0.045	0.723	0.660	0.1516	8.7941
14.0	0.755	0.045	0.710	0.644	0.1480	8.8185
15.0	0.740	0.045	0.695	0.625	0.1437	8.8475
17.0	0.736	0.045	0.691	0.620	0.1426	8.8553
21.0	0.714	0.045	0.669	0.593	0.1364	8.8997
23.0	0.704	0.045	0.659	0.581	0.1336	8.9206
25.0	0.680	0.045	0.635	0.552	0.1269	8.9725
27.0	0.665	0.045	0.620	0.533	0.1226	9.0063
29.0	0.660	0.045	0.615	0.527	0.1212	9.0178
35.0	0.640	0.045	0.595	0.503	0.1156	9.0654

TABLE XXII (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-Log_e\ (C)_t$
37.0	0.630	0.045	0.585	0.491	0.1128	9.0900
50.0	0.560	0.045	0.515	0.405	0.0931	9.2820
75.0	0.498	0.045	0.453	0.329	0.0756	9.4896
93.0	0.455	0.045	0.410	0.276	0.0635	9.6640
120.0	0.385	0.045	0.340	0.191	0.0438	10.0352

$*(A_T)_t = A_E - A_{sol}$

Weight of ester $\underset{\sim}{1a}$ dissolved in 25 mL of D_2O = 1.40 mg (1.2 μL)

Temp = 25 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 4350\ M^{-1}cm^{-1}$; $\varepsilon_2 = 800\ M^{-1}cm^{-1}$; $(pH)_{average} = 4.41$;

Number of data points = 26

Experiment #1

$(C_{\underset{\sim}{1a}})_o = 0.2312$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.1864$ mM; $k_{obs} = 20.8 \times 10^{-5} sec^{-1}$; $R^2 = 0.966$

TABLE XXII (Continued)

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.3188$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.2433$ mM; $k_{obs} = 14.7 \times 10^{-5}\text{sec}^{-1}$; $R^2 = 0.969$

Combining the data from Table XXI

#1 $k_{H_2O} / k_{D_2O} = 32.4 \times 10^{-5}\text{sec}^{-1} / 20.8 \times 10^{-5}\text{sec}^{-1} = \underline{1.56}$

#2 $k_{H_2O} / k_{D_2O} = 23.4 \times 10^{-5}\text{sec}^{-1} / 14.7 \times 10^{-5}\text{sec}^{-1} = \underline{1.59}$

Evaluation of Activation Parameters (Runs 11-17)

In order to evaluate the temperature dependence of the reaction rate constant, rates of hydrolysis of ester 1a in 0.265 mM hydrochloric acid were measured at the following temperatures: Run 11, 20°C; Run 12, 27.5°C; Run 13, 32.5°C; and Run 14, 35°C. Solvent selection required 0.265 mM hydrochloric acid so that the magnitude of hydrolysis rates would be suitable for convenient measurements.

Rates of hydrolysis of ester 1a in H_2O in the absence of any external acid were also measured at the following temperatures: Run 15, 30°C; Run 16, 32.2°C; and Run 17, 35.5°C. Experiments were performed exactly as described before. Every run was performed in duplicate. Results are summarized in Tables XXIII - XXIX.

For the evaluation of k'_{obs} (defined as $k_{obs}\, C_{H_3O^+}$) from runs made in 0.265 hydrochloric acid solutions, $C_{H_3O^+}$ was calculated from C°_{HCl}. For runs made in H_2O, a value of $C_{H_3O^+}$ was derived from the experimentally observed average pH value of 4.4 ± 0.05 measured during the course of the reaction. The sudden fall of pH (from 6.5-4.5) observed in the aqueous solution of ester 1a in the absence of external acid during the initial stages (10-15%) of the reaction was ignored while computing the value of k'_{obs}. The activation energy (E_a) and the pre-exponential factor (A') were evaluated from the Arrhenius Eq. (60)

$$k'_{obs} = A' e^{-E_a/RT} \tag{60}$$

where

$$k'_{obs} = \frac{k_{obs} \cdot C_{H_3O^+}}{C^n_{H_2O}} \quad (n=0) \tag{61}$$

TABLE XXIII

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.265 mM HYDROCHLORIC ACID AT 20°C; RUN 11*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\text{Log}_e\ (C)_t$
6.5	1.200	0.055	1.145	1.122	0.2069	8.4835
33.0	1.195	0.055	1.140	1.116	0.2058	8.4888
70.0	1.140	0.055	1.085	1.051	0.1938	8.5485
152.0	1.065	0.055	1.010	0.963	0.1776	8.6363
222.0	0.978	0.055	0.923	0.860	0.1587	8.7487
387.0	0.840	0.050	0.790	0.704	0.1298	8.9496
514.0	0.738	0.057	0.681	0.576	0.1061	9.1508
817.0	0.576	0.060	0.516	0.381	0.0703	9.5625
1287.0	0.425	0.050	0.375	0.216	0.0397	10.1338
1590.0	0.380	0.055	0.325	0.157	0.0289	10.4530
2398.0	0.295	0.055	0.240	0.056	0.0104	11.4727

$*(A_T)_t = A_E - A_{sol}$

Weight of ester 1a dissolved in 100 mL of 0.265 mM hydrochloric acid = 5.70 mg

Temp = 20 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 5425\ M^{-1}cm^{-1}$; $\varepsilon_2 = 815\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.6 \pm 0.03$;

Number of data points = 11

TABLE XXIII (Continued)

Experiment #1

$(C_{\underset{\sim}{1a}})_o = 0.2353$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.2092$ mM; $k_{obs} = 2.10 \times 10^{-5}\text{sec}^{-1}$; $R^2 = 0.999$

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.2374$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.2134$ mM; $k_{obs} = 2.20 \times 10^{-5}\text{sec}^{-1}$; $R^2 = 0.998$

k_{obs}(average) = $(2.15 \pm 0.07) \times 10^{-5}\text{sec}^{-1}$

TABLE XXIV

THE RATE OF HYDROLYSIS OF ESTER 1a IN 0.265 mM HYDROCHLORIC ACID AT 27.5°C; RUN 12*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\text{Log}_e\ (C)_t$
6.0	1.280	0.050	1.230	1.230	0.2268	8.3916
15.0	1.250	0.050	1.200	1.194	0.2202	8.4207
25.0	1.200	0.050	1.150	1.136	0.2094	8.4713
39.0	1.160	0.050	1.110	1.088	0.2007	8.5136
52.0	1.105	0.050	1.055	1.024	0.1888	8.5749
70.0	1.060	0.050	1.010	0.971	0.1790	8.6281
90.0	1.000	0.050	0.950	0.900	0.1660	8.7036
110.0	0.942	0.050	0.892	0.832	0.1534	8.7824
130.0	0.893	0.050	0.843	0.774	0.1428	8.8543
152.0	0.846	0.050	0.796	0.719	0.1326	8.9284
175.0	0.792	0.050	0.742	0.655	0.1209	9.0210
204.0	0.735	0.050	0.685	0.588	0.1085	9.1290
238.0	0.676	0.050	0.626	0.519	0.0957	9.2546
268.0	0.630	0.050	0.580	0.465	0.0857	9.3648
318.0	0.564	0.050	0.514	0.387	0.0714	9.5478
368.0	0.518	0.050	0.468	0.333	0.0614	9.6985
418.0	0.476	0.050	0.426	0.283	0.0523	9.8593
482.0	0.438	0.050	0.388	0.239	0.0440	10.0310
541.0	0.398	0.048	0.350	0.194	0.0358	10.2385
599.0	0.372	0.050	0.322	0.161	0.0297	10.4247

TABLE XXIV (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e\ (C)_t$
742.0	0.324	0.048	0.276	0.107	0.0197	10.8346
915.0	0.298	0.050	0.248	0.074	0.0136	11.2034

$*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 0.265 mM hydrochloric acid = 5.50 mg

Temp = 27.5 ± 0.1°C; λ = 268 nm; $\varepsilon_1 = 5425\ M^{-1}cm^{-1}$; $\varepsilon_2 = 815\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.6 \pm 0.03$;

Number of data points = 22

Experiment #1

$(C_{\mathbf{1a}})_o = 0.2271$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2170$ mM; $k_{obs} = 5.40 \times 10^{-5} sec^{-1}$; $R^2 = 0.994$

Experiment #2

$(C_{\mathbf{1a}})_o = 0.2333$ mM; $\left[(C_{\mathbf{1a}})_o\right]_{calc} = 0.2175$ mM; $k_{obs} = 5.52 \times 10^{-5} sec^{-1}$; $R^2 = 0.994$

$k_{obs}(\text{average}) = (5.46 \pm 0.08) \times 10^{-5} sec^{-1}$

TABLE XXV

THE RATE OF HYDROLYSIS OF ESTER **1a** IN 0.265 mM HYDROCHLORIC ACID AT 32.5°C; RUN 13*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\text{Log}_e\ (C)_t$
6.0	1.274	0.050	1.224	1.215	0.2240	8.4039
14.0	1.235	0.050	1.185	1.169	0.2155	8.4424
20.0	1.192	0.050	1.142	1.118	0.2062	8.4867
27.0	1.130	0.050	1.080	1.045	0.1928	8.5541
34.0	1.110	0.050	1.060	1.022	0.1884	8.5769
43.0	1.075	0.050	1.025	0.981	0.1808	8.6181
53.0	1.012	0.050	0.962	0.906	0.1671	8.6967
61.0	0.985	0.050	0.935	0.875	0.1613	8.7324
72.0	0.930	0.050	0.880	0.810	0.1493	8.8093
82.0	0.880	0.050	0.830	0.751	0.1385	8.8848
94.0	0.840	0.050	0.790	0.704	0.1298	8.9495
108.0	0.795	0.050	0.745	0.651	0.1200	9.0277
122.0	0.750	0.050	0.700	0.598	0.1103	9.1126
138.0	0.700	0.050	0.650	0.539	0.0994	9.2162
156.0	0.662	0.050	0.612	0.494	0.0912	9.3028
180.0	0.610	0.050	0.560	0.433	0.0799	9.4349
220.0	0.536	0.050	0.486	0.346	0.0638	9.6594
261.0	0.475	0.050	0.425	0.274	0.0506	9.8919
310.0	0.420	0.045	0.375	0.215	0.0397	10.1334
344.0	0.400	0.050	0.350	0.186	0.0343	10.2802

TABLE XXV (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-\mathrm{Log}_e\ (C)_t$
400.0	0.350	0.050	0.300	0.127	0.0235	10.6605
464.0	0.320	0.048	0.272	0.094	0.0174	10.9605

$*(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of 0.265 mM hydrochloric acid = 5.70 mg

Temp = 32.5 ± 0.1°C; λ = 268 nm; ε_1 = 5425 $M^{-1}cm^{-1}$; ε_2 = 815 $M^{-1}cm^{-1}$; $(pH)_{average}$ = 3.6 ± 0.03;

Number of data points = 22

Experiment #1

$(C_{\mathbf{1a}})_o$ = 0.2353 mM; $\left((C_{\mathbf{1a}})_o\right)_{calc}$ = 0.2243 mM; k_{obs} = 9.34 × $10^{-5}sec^{-1}$; R^2 = 0.999

Experiment #2

$(C_{\mathbf{1a}})_o$ = 0.2333 mM; $\left((C_{\mathbf{1a}})_o\right)_{calc}$ = 0.2225 mM; k_{obs} = 9.26 $10^{-5}sec^{-1}$; R^2 = 0.998

k_{obs}(average) = (9.30 ± 0.06) × $10^{-5}sec^{-1}$

TABLE XXVI

THE RATE OF HYDROLYSIS OF ESTER **1a** IN 0.265 mM HYDROCHLORIC ACID AT 35°C; RUN 14*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\text{Log}_e\ (C)_t$
4.0	1.130	0.050	1.080	1.041	0.1920	8.5579
9.0	1.125	0.050	1.075	1.035	0.1909	8.5636
17.0	1.108	0.050	1.058	1.015	0.1873	8.5831
24.0	1.104	0.050	1.054	1.011	0.1864	8.5877
37.0	0.970	0.050	0.920	0.853	0.1573	8.7574
47.0	0.920	0.050	0.870	0.794	0.1465	8.8288
61.0	0.850	0.050	0.800	0.712	0.1313	8.9384
75.0	0.790	0.050	0.740	0.641	0.1182	9.0428
90.0	0.728	0.050	0.678	0.568	0.1048	9.1636
105.0	0.678	0.050	0.628	0.509	0.0939	9.2730
121.0	0.632	0.050	0.582	0.455	0.0840	9.3853
144.0	0.570	0.050	0.520	0.382	0.0705	9.5600
169.0	0.520	0.050	0.470	0.323	0.0596	9.7271
192.0	0.480	0.050	0.430	0.276	0.0510	9.8844
213.0	0.450	0.050	0.400	0.241	0.0445	10.0211
223.0	0.420	0.050	0.370	0.206	0.0379	10.1795
251.0	0.400	0.050	0.350	0.182	0.0336	10.3010
275.0	0.375	0.050	0.325	0.153	0.0282	10.4771
302.0	0.350	0.050	0.300	0.123	0.0228	10.6910
340.0	0.320	0.050	0.270	0.088	0.0162	11.0281

TABLE XXVI (Continued)

$*(A_T)_t = A_E - A_{sol}$

Weight of ester 1a dissolved in 100 mL of 0.265 mM hydrochloric acid = 5.80 mg

Temp = 35 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 5425\ M^{-1}cm^{-1}$; $\varepsilon_2 = 815\ M^{-1}cm^{-1}$; $(pH)_{average} = 3.6 \pm 0.03$;

Number of data points = 20

Experiment #1

$(C_{1a})_o = 0.2395$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2069$ mM; $k_{obs} = 12.28 \times 10^{-5} sec^{-1}$; $R^2 = 0.998$

Experiment #2

$(C_{1a})_o = 0.2436$ mM; $\left[(C_{1a})_o\right]_{calc} = 0.2048$ mM; $k_{obs} = 12.23 \times 10^{-5} sec^{-1}$; $R^2 = 0.999$

k_{obs}(average) = $(12.26 \pm 0.04) \times 10^{-5} sec^{-1}$

TABLE XXVII

THE RATE OF HYDROLYSIS OF ESTER **1a** IN WATER AT 30°C; RUN 15*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\text{Log}_e\ (C)_t$
3.5	0.945	0.050	0.895	0.870	0.2000	8.5170
4.0	0.922	0.050	0.872	0.842	0.1936	8.5499
5.0	0.876	0.050	0.826	0.786	0.1806	8.6192
6.0	0.854	0.050	0.804	0.759	0.1744	8.6540
7.0	0.824	0.050	0.774	0.722	0.1660	8.7037
8.0	0.790	0.050	0.740	0.680	0.1564	8.7630
9.0	0.780	0.050	0.730	0.668	0.1536	8.7812
10.0	0.760	0.050	0.710	0.644	0.1480	8.8185
11.0	0.740	0.050	0.690	0.619	0.1423	8.8573
12.5	0.710	0.050	0.660	0.582	0.1339	8.9185
13.5	0.682	0.050	0.632	0.548	0.1260	8.9791
15.0	0.670	0.050	0.620	0.533	0.1226	9.0063
16.0	0.660	0.050	0.610	0.521	0.1198	9.0295
17.0	0.650	0.050	0.600	0.509	0.1170	9.0533
18.0	0.640	0.050	0.590	0.497	0.1142	9.0776
19.5	0.620	0.050	0.570	0.472	0.1086	9.1282
22.0	0.570	0.050	0.520	0.411	0.0945	9.2670
24.5	0.562	0.050	0.512	0.401	0.922	9.2911
26.0	0.555	0.050	0.505	0.393	0.0903	9.3127
28.0	0.540	0.050	0.490	0.374	0.0861	9.3606
30.0	0.526	0.050	0.476	0.357	0.0821	9.4075

TABLE XXVII (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol L^{-1} × 10^3)	$-Log_e\ (C)_t$
32.0	0.516	0.050	0.466	0.345	0.0793	9.4424
34.0	0.500	0.050	0.450	0.325	0.0748	9.5009
36.0	0.498	0.050	0.448	0.323	0.0742	9.5084
38.0	0.476	0.050	0.426	0.296	0.0680	9.5955
40.0	0.464	0.050	0.414	0.281	0.0647	9.6464
42.5	0.440	0.050	0.390	0.252	0.0579	9.7568
48.0	0.420	0.050	0.370	0.227	0.0523	9.8591
50.0	0.410	0.050	0.360	0.215	0.0495	9.9144
54.0	0.400	0.050	0.350	0.203	0.0466	9.9730
58.0	0.382	0.050	0.332	0.181	0.0416	10.0880
62.0	0.370	0.050	0.320	0.166	0.0382	10.1727
70.0	0.348	0.050	0.298	0.139	0.0320	10.3495

$*(A_T)_t = A_E - A_{sol}$

Weight of ester $\underset{\sim}{1a}$ dissolved in 100 mL of distilled water = 5.60 mg

Temp = 30 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 4350\ M^{-1}cm^{-1}$; $\varepsilon_2 = 800\ M^{-1}cm^{-1}$; $(pH)_{average} = 4.4$;

Number of data points = 33

TABLE XXVII (Continued)

Experiment #1

$(C_{\underset{\sim}{1a}})_o = 0.2312$ mM; $\left((C_{\underset{\sim}{1a}})_o\right)_{calc} = 0.1918$ mM; $k_{obs} = 44.93 \times 10^{-5}\text{sec}^{-1}$; $R^2 = 0.986$

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.2312$ mM; $\left((C_{\underset{\sim}{1a}})_o\right)_{calc} = 0.1906$ mM; $k_{obs} = 43.08 \times 10^{-5}\text{sec}^{-1}$; $R^2 = 0.986$

$k_{obs}(\text{average}) = (44.0 \pm 1.3) \times 10^{-5}\text{sec}^{-1}$

TABLE XXVIII

THE RATE OF HYDROLYSIS OF ESTER 1a IN WATER AT 32.2°C; RUN 16*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\text{Log}_e\ (C)_t$
3.5	0.880	0.050	0.830	0.791	0.1817	8.6129
4.0	0.862	0.050	0.812	0.769	0.1767	8.6412
4.5	0.845	0.050	0.795	0.748	0.1719	8.6687
5.0	0.825	0.050	0.775	0.723	0.1663	8.7020
5.5	0.805	0.050	0.755	0.699	0.1606	8.7364
6.0	0.790	0.050	0.740	0.680	0.1564	8.7630
6.5	0.770	0.050	0.720	0.656	0.1508	8.7997
7.0	0.755	0.050	0.705	0.638	0.1466	8.8281
7.5	0.742	0.050	0.692	0.622	0.1429	8.8534
8.0	0.730	0.050	0.680	0.607	0.1395	8.8773
8.5	0.715	0.050	0.665	0.589	0.1353	8.9080
9.5	0.684	0.050	0.634	0.551	0.1266	8.9747
10.0	0.680	0.050	0.630	0.546	0.1255	8.9836
11.0	0.666	0.050	0.616	0.529	0.1215	9.0155
12.0	0.642	0.050	0.592	0.499	0.1148	9.0727
13.0	0.626	0.050	0.576	0.480	0.1102	9.1128
14.5	0.580	0.050	0.530	0.423	0.0973	9.2377
15.0	0.572	0.050	0.522	0.413	0.0951	9.2611
16.5	0.568	0.050	0.518	0.409	0.0939	9.2730
17.5	0.555	0.050	0.505	0.393	0.0903	9.3127
19.0	0.536	0.050	0.486	0.369	0.0849	9.3738

TABLE XXVIII (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e\ (C)_t$
20.5	0.522	0.050	0.472	0.352	0.0810	9.4213
22.0	0.506	0.050	0.456	0.333	0.0765	9.4785
23.5	0.490	0.050	0.440	0.313	0.0720	9.5392
25.0	0.476	0.050	0.426	0.296	0.0680	9.5955
27.0	0.459	0.050	0.409	0.275	0.0633	9.6684
29.0	0.446	0.050	0.396	0.259	0.0596	9.7280
31.0	0.432	0.050	0.382	0.242	0.0557	9.7964
33.0	0.410	0.050	0.360	0.215	0.0495	9.9144
35.0	0.400	0.050	0.350	0.203	0.0466	9.9730
38.0	0.372	0.050	0.322	0.169	0.0388	10.1581
41.0	0.365	0.050	0.315	0.160	0.0368	10.2102
44.0	0.350	0.050	0.300	0.142	0.0326	10.3321
47.0	0.340	0.050	0.290	0.129	0.0298	10.4225
51.0	0.320	0.050	0.270	0.105	0.0241	10.6322
55.0	0.310	0.050	0.260	0.093	0.0213	10.7562
60.0	0.302	0.050	0.252	0.083	0.0191	10.8679

*$(A_T)_t = A_E - A_{sol}$

Weight of ester **1a** dissolved in 100 mL of distilled water = 5.60 mg

TABLE XXVIII (Continued)

Temp = 32.2 ± 0.2°C; λ = 268 nm; $\varepsilon_1 = 4350\ M^{-1}cm^{-1}$; $\varepsilon_2 = 800\ M^{-1}cm^{-1}$; $(pH)_{average} = 4.4$;

Number of data points = 37

Experiment #1

$(C_{\underset{\sim}{1a}})_o = 0.2312$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.1912$ mM; $k_{obs} = 67.2 \times 10^{-5} sec^{-1}$; $R^2 = 0.993$

Experiment #2

$(C_{\underset{\sim}{1a}})_o = 0.2436$ mM; $\left[(C_{\underset{\sim}{1a}})_o\right]_{calc} = 0.2095$ mM; $k_{obs} = 59.6 \times 10^{-5} sec^{-1}$; $R^2 = 0.991$

$k_{obs}(average) = (63.4 \pm 5.4) \times 10^{-5} sec^{-1}$

TABLE XXIX

THE RATE OF HYDROLYSIS OF ESTER 1a IN WATER AT 35.5°C; RUN 17*

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\mathrm{Log}_e\ (C)_t$
3.5	0.870	0.050	0.820	0.776	0.1785	8.6311
4.0	0.850	0.050	0.800	0.752	0.1728	8.6632
4.5	0.825	0.050	0.775	0.721	0.1658	8.7048
5.0	0.805	0.050	0.755	0.697	0.1602	8.7393
5.5	0.779	0.050	0.729	0.665	0.1529	8.7861
6.0	0.760	0.050	0.710	0.642	0.1475	8.8217
6.5	0.740	0.050	0.690	0.617	0.1419	8.8606
7.0	0.725	0.050	0.675	0.599	0.1377	8.8908
7.5	0.705	0.050	0.655	0.574	0.1320	8.9325
8.5	0.670	0.050	0.620	0.531	0.1222	9.0101
9.5	0.654	0.050	0.604	0.512	0.1177	9.0476
10.0	0.640	0.050	0.590	0.495	0.1137	9.0817
11.0	0.615	0.050	0.565	0.464	0.1067	9.1456
13.5	0.560	0.050	0.510	0.397	0.0912	9.3023
15.5	0.530	0.050	0.480	0.360	0.0828	9.3995
17.0	0.508	0.050	0.458	0.333	0.0766	9.4772
19.0	0.482	0.050	0.432	0.301	0.0693	9.5777
21.0	0.460	0.050	0.410	0.274	0.0631	9.6713
23.0	0.432	0.050	0.382	0.240	0.0552	9.8048
25.0	0.410	0.050	0.360	0.213	0.0490	9.9238
27.0	0.400	0.050	0.350	0.201	0.0462	9.9830

TABLE XXIX (Continued)

Time (t) (min)	Absorbance A_E	Base-line reading with solvent A_{sol}	Absorbance $(A_T)_t$	Absorbance of substrate $(A_s)_t$	Concentration of substrate $(C)_t$ (mol $L^{-1} \times 10^3$)	$-\text{Log}_e\ (C)_t$
29.5	0.377	0.050	0.327	0.173	0.0397	10.1340
31.0	0.365	0.050	0.315	0.158	0.0363	10.2229
33.0	0.355	0.050	0.305	0.146	0.0335	10.3035
35.0	0.345	0.050	0.295	0.134	0.0307	10.3913
40.0	0.320	0.050	0.270	0.103	0.0237	10.6516

$^*(A_T)_t = A_E - A_{sol}$

Weight of ester la dissolved in 100 mL of distilled water = 5.65 mg

Temp = 35.5 ± 0.1°C; $\lambda = 268$ nm; $\varepsilon_1 = 4350\ M^{-1}cm^{-1}$; $\varepsilon_2 = 800\ M^{-1}cm^{-1}$; $(pH)_{average} = 4.4$;

Number of data points = 26

Experiment #1

$(C_{la})_o = 0.2333$ mM; $\left[(C_{la})_o\right]_{calc} = 0.2028$ mM; $k_{obs} = 92.0 \times 10^{-5} sec^{-1}$; $R^2 = 0.997$ and for duplicate run

Experiment #2

$(C_{la})_o = 0.2271$ mM; $\left[(C_{la})_o\right]_{calc} = 0.1863$ mM; $k_{obs} = 102.0 \times 10^{-5} sec^{-1}$; $R^2 = 0.995$

k_{obs}(average) = $(97.0 \pm 7.1) \times 10^{-5} sec^{-1}$

An Arrhenius plot for $\log_e k'_{obs}$ [defined by Eq. (61)] versus 1/T is given in Figure 7. Values of E_a and A' were found to be: $E_a = 20.5$ kcal/mol and $\log_e A' = 16.25$ (n = 0); 12.23 (n = 1); 8.22 (n = 2); and 4.20 (n = 3) since $C_{H_2O} = 55.56$ mol L^{-1}. Data from which E_a and A' were evaluated could be seen in Table XXX. An evaluation of $\Delta H^{\ddagger}$ and $\Delta S^{=}$ from Arrhenius parameters E_a and A' was initiated. From the Eyring Eq. [Eq. (62)],[33] we have:

$$k'_{rate} = \frac{KkT}{h} e^{\frac{-\Delta H^{\ddagger}}{RT}} e^{\frac{\Delta S^{\ddagger}}{RT}} \tag{62}$$

where

k_{rate} = rate constant (k'_{obs})

K = transmission coefficient assumed to be unity

k = Boltzmann constant (1.38×10^{-16} erg K^{-1} mol^{-1})

T = Temperature in K

h = Planck's constant (6.63×10^{-27} erg sec)

$\Delta H^{\ddagger}$ = enthalpy of activation in kcal mol^{-1}

$\Delta S^{\ddagger}$ = entropy of activation in eu and

R = gas constant (1.987 cal K^{-1} mol^{-1})

Comparing Eqs. (60), (61) and (62) and for a reaction occurring in any solution and assuming $\Delta S^{\ddagger} \neq f(T)$, it can be shown[49] that

$$E_a = \Delta H^{\ddagger} + RT \tag{63}$$

and

$$A' = \frac{KkTe}{h} e^{\Delta S^{\ddagger}/R} \tag{64}$$

Substituting the appropriate values for the parameters in Eq. (63) and (64) we have:

TABLE XXX

EVALUATION OF ARRHENIUS PARAMETERS*

Run	Temp. ± 0.1°C	T(K)	$1/T \times 10^3$ (k^{-1})	$k_{obs} \times 10^5$ (sec^{-1})	$k'_{obs} \times 10^{8}$[a] ($sec^{-1} mol\ L^{-1}$)	$-Log_e\ k'_{obs}$
11	20.0	293.16	3.411	2.15	0.57	18.98
2	25.0	298.16	3.354	4.31	1.14	18.29
12	27.5	300.66	3.326	5.46	1.45	18.05
13	32.5	305.66	3.272	9.30	2.46	17.52
14	35.0	308.16	3.245	12.26	3.25	17.24
9	25.0	298.16	3.354	32.10	1.28	18.17
15	30.0	303.16	3.299	44.00	1.75	17.86
16	32.2	305.36	3.275	63.40	2.52	17.50
17	35.5	308.66	3.240	97.00	3.86	17.07

*E_a = 20.5 k cal mol^{-1} $Log_e A'$ = 16.25(n=0)[a] R^2 = 0.982 (0.996)[b]

[a] $k'_{obs} = k_{obs} C_{H_3O^+} / C^n_{H_2O}$ and $C_{H_3O^+} = C^\circ_{HCl}$ = 0.265 mM for runs made in HCl (runs 2, 11, 12, 13 and 14). For runs made in H_2O, (runs 9, 15, 16 and 17) $C_{H_3O^+}$ was calculated from the experimentally observed average pH = 4.4.

[b] Value in parentheses was obtained if data from runs made in HCl (runs 2, 11, 12, 13 and 14) alone were used. Corresponding values of E_a and $log_e A'$ were found to differ from the reported values only in the 3rd significant figures. For evaluation of errors in E_a and A' see discussion under Error Analysis.

$$\Delta H^{\ddagger} = 20.5 - 300.91 \times 1.987 \times 10^{-3} \text{ kcal mol}^{-1} = 19.9 \text{ kcal mol}^{-1}$$

Equation (64) can be written as

$$\Delta S^{\dagger} = R\{\log_e A' - \log_e kT/h - 1\} \; (K = 1) \tag{65}$$

$\log_e kT/h = 29.47$ for $T = 300.9$ K. Substituting this value of kT/h into Eq. (65):

$$\Delta S^{\dagger} = \{-29.47 - 1 + \log_e A'\}R \text{ eu} \tag{66}$$

Substituting the values of $\log_e A'$ for n = 2 or n = 3 [Eq. (61)] evaluated earlier into Eq. (66) we have:

$$\Delta S^{\dagger} = \{-29.47 - 1 + 8.22\}\, 1.987 \text{ eu} = -44.2 \text{ eu } (n = 2)$$

$$\Delta S^{\dagger} = \{-29.47 - 1 + 4.20\}\, 1.987 \text{ eu}$$

$$\Delta S^{\dagger} = -52.2 \text{ eu (for } n = 3). \tag{67}$$

Error Analysis

Psuedo first-order rate constants were evaluated from Eq. (41) and (42) by the method of least squares. Results are summarized in Table V (see page 57). Figures 3 and 4 (see pages 49 and 51) represent typical first-order plots. Figure 3 also represents the pH variation in aqueous solutions of **1a** in the absence of any external acid. In water, a higher initial rate was observed during the first 10-15% of the reaction time (Figure 3). This could be due to the initial abrupt fall in pH observed during this period of reaction, after which a steady state was attained (may be due to self protonation of the reactant by benzoic acid (**27a**) produced initially). No such higher initial rate was detected in acid (HCl) solutions of **1a** (Figure 4). The pH of solutions of **1a** in all the hydrochloric acid solutions studied, which were monitored to four half lives, was found to be reasonably constant (± 0.03). The average value of the pH observed in acid solutions of $\underset{\sim}{1a}$ was also found to correspond to C°_{HCl} initial concentration within experimental error.

Examining the data presented in Table V, it is clear that the least squares correlation coefficient R^2 is close to unity in all cases. The initial concentration of ester $\underset{\sim}{1a}$ calculated from the least squares intercept agrees fairly well with experimental values in acid solutions. In water, the calculated values of $(C_{\underset{\sim}{1a}})_o$ were always found to be less than the experimental values at least by 20%. This could be the result of the higher initial rate in water which was found to be absent in acid solutions. A maximum deviation of 6% was observed in the rate constants (k_{obs}) determined from forty independent runs. Only two independent duplicate runs were made at each concentration where the rate constants differed only by ±2% or less. More runs were made when the deviation in rate constant exceeded 2%. In those cases where no external acid was added, the deviations in k_{obs} were found to be greater as compared with the observed deviation in k_{obs} in the acid solutions. Data reported in Table V represent the rate constants with an average standard deviation of ±5%.

It was found that the rate constants were not sensitive to the values of ε_1. This resulted because the rate constants were derived using Eqs. (41) and (42) (from the ratio of $(C)_t$ at different intervals

$$-\log_e(C)_t = -\log_e(C)_o + k_{obs}t \qquad (41)$$

$$(C)_t = \frac{(A_T)_t - \varepsilon_2(C_{\underset{\sim}{1a}})_o}{\varepsilon_1 - \varepsilon_2} \qquad (42)$$

of time t) and the denominator in Eq. (42) cancels out when the Eqs. are combined as shown in Eq. (68).

$$k_{obs} = \frac{1}{t_2 - t_1} \log_e \frac{[(A_T)_{t_1} - \varepsilon']}{[(A_T)_{t_2} - \varepsilon']} \tag{68}$$

where ε' is given by Eq. (69).

$$\varepsilon' = (C_{\underset{\sim}{1a}})_o \, \varepsilon_2 \tag{69}$$

(ℓ = 1 cm and is not explicitly shown in the Eqs.)

However, computation of a reliable rate constant would require a known accurate value of ε_2 which was easier to evaluate. An estimated maximum error of 6% in the product $(C_{\underset{\sim}{1a}})_o \, \varepsilon_2$ was found to give rise to an error of 4% in the final rate constant by numerical calculation.

A detailed error analysis was done as follows. To evaluate the standard deviation in k_{obs} ($\sigma_{k_{obs}}/k_{obs}$) in terms of the standard deviations in the variables t_1, t_2, $(A_T)_{t_1}$, $(A_T)_{t_2}$ and ε', one can proceed to evaluate the partial differentials of k_{obs} with respect to each of the above variables. Also $\sigma_{k_{obs}}/k_{obs}$ is given by Eq. (70) assuming that all inconsistencies arise from random errors and errors in each variable are independent of the error in other variables (i.e., cross terms in the error function are neglected).[18]

$$\sigma_{k_{obs}} = \left\{ \left[\left(\frac{\partial k_{obs}}{\partial t_1} \right)^2_{t_2, A_{t_1}, A_{t_2}, \varepsilon'} \right] \sigma^2_{t_1} + \left[\left(\frac{\partial k_{obs}}{\partial t_2} \right)^2_{t_1, A_{t_1}, A_{t_2}, \varepsilon'} \right] \sigma^2_{t_2} + \left[\left(\frac{\partial k_{obs}}{\partial A_{t_1}} \right)^2_{t_1, t_2, A_{t_2}, \varepsilon'} \right] \sigma^2_{A_{t_1}} + \left[\left(\frac{\partial k_{obs}}{\partial A_{t_2}} \right)^2_{t_1, t_2, A_{t_1}, \varepsilon'} \right] \sigma^2_{A_{t_2}} + \left[\left(\frac{\partial k_{obs}}{\partial \varepsilon'} \right)^2_{t_1, t_2, A_{t_1}, A_{t_2}} \right] \sigma_{\varepsilon'} \right\}^{\frac{1}{2}} \quad (70)$$

$(A_T)_{t_1}$ and $(A_T)_{t_2}$ are abbreviated as A_{t_1} and A_{t_2}, respectively, for convenience. Now, assuming that the errors in t_1 and $t_2(\sigma_t)$ do not depend upon the size of t_1 or t_2 and similarly errors in A_{t_1} and A_{t_2} (σ_A) do not depend upon the size of A_{t_1} and A_{t_2}, one can write Eqs:

$$\sigma_{t_1} = \sigma_{t_2} = \sigma_t \quad (71)$$

$$\sigma_{A_{t_1}} = \sigma_{A_{t_2}} = \sigma_A \quad (72)$$

Making the following substitutions

$$\log \frac{[A_{t_1} - \varepsilon']}{[A_{t_2} - \varepsilon']} = \phi \quad (73)$$

$$(A_{t_1} - \varepsilon') = \theta_1 \quad (74)$$

$$(A_{t_2} - \varepsilon') = \theta_2 \quad (75)$$

and evaluating the partial differentials for k_{obs} from Eq. (68) and combining Eqs. (70), (71), (72), (73), (74), and (75), the standard deviation in k_{obs} is given by Eq. (76):

$$\frac{\sigma_{k_{obs}}}{k_{obs}} = \left\{ \frac{2\sigma_t^2}{(t_2 - t_1)^2} + \phi^{-2}\left(\frac{1}{\theta_1^2} + \frac{1}{\theta_2^2}\right)\sigma_A^2 + \phi^{-2}\left(\frac{1}{\theta_2} - \frac{1}{\theta_1}\right)^2 \sigma_{\varepsilon'}^2 \right\}^{\frac{1}{2}} \tag{76}$$

Defining the error functions such that:

$$E_t = \frac{2\sigma_t^2}{(t_2 - t_1)^2} \tag{77}$$

$$E_A = \phi^{-2}\left(\frac{1}{\theta_1^2} + \frac{1}{\theta_2^2}\right)\sigma_A^2 \tag{78}$$

and

$$E_{\varepsilon'} = \phi^{-2}\left(\frac{1}{\theta_2} - \frac{1}{\theta_1}\right)^2 \sigma_{\varepsilon'}^2 \tag{79}$$

and substituting these values in Eq. (76) we have:

$$\frac{\sigma_{k_{obs}}}{k_{obs}} = [E_t + E_A + E_{\varepsilon'}]^{\frac{1}{2}} \tag{80}$$

Each term (E_t, E_A and $E_{\varepsilon'}$) in Eq. (80) is a measure of the contribution to the total error in k_{obs} arising from errors in t, A and ε', respectively. Thus, one could approximately estimate the error in k_{obs} in terms of the errors in t, A and ε' from Eq. (80).

Taking as a specific test case, Run 4, from the data set in Table XV (for the rate of hydrolysis of $\underset{\sim}{1a}$ in 0.795 mM hydrochloric acid at 25°C), values of $\sigma_{k_{obs}}/k_{obs}$ were calculated using estimated values for σ_t, σ_A and $\sigma_{\varepsilon'}$. Thus, k_{obs} was evaluated for nine pairs of readings chosen at time intervals which were fairly separated (it is clear from the mathematical form of the error functions that the error enhances considerably as $t_1 \rightarrow t_2$). The following values were used for σ_t, σ_A and $\sigma_{\varepsilon'}$ in the computation of $\sigma_{k_{obs}}$:σ_t = 0.2 min (estimated value) σ_A = 0.005 (experimentally observed) and $\sigma_{\varepsilon'}$ = 0.01 (since by definition $\varepsilon' = (C_{\underset{\sim}{1a}})_o\ \varepsilon_2$, relative error in ε' was computed from the sum of the experimentally observed relative errors in $(C_{\underset{\sim}{1a}})_o$ and ε_2 which were found to be 1% and 4%, respectively. Since $\varepsilon' = 875 \times 0.2312 \times 10^{-3}$ = 0.202 and the relative error in $\varepsilon' = \sigma_{\varepsilon'}/\varepsilon'$ = 5%, $\sigma_{\varepsilon'}$ was evaluated from $\sigma_{\varepsilon'} = 0.202 \times 0.05 = 0.01$). The experimental standard deviation in k_{obs} (2.1%) was found to be less than the computed average standard deviation (3.07%) (see Table XXXI). It is also clear from the data on Table XXXI, that, as the size of A_t decreases, the error in k_{obs} arising from the error in ε' becomes more significant. Contributions from an error from A_t are comparatively small. An error in k_{obs} arising from errors in t is negligible if t_1 and t_2 are so chosen so as to make the difference $(t_2 - t_1)$ large enough compared to σ_t as in the above example. An error in k_{obs} stemming from errors in temperature measurements could be evaluated by the same method by differentiating the Arrhenius Eq.

$$k_{obs} = A' e^{-E_a/RT}$$

TABLE XXXI

EVALUATION OF ERROR IN k_{obs}*

t_1 (min)	t_2 (min.)	$k_{obs} \times 10^5$ (sec^{-1})	ϕ^a	$\theta_1{}^a$	$\theta_2{}^a$	$E^a_t \times 10^7$	$E^a_A \times 10^4$	$E^a_{\varepsilon'} \times 10^4$	$\frac{\sigma^a_{k_{obs}}}{k_{obs}}$
4.0	520.0	1.546	0.4784	1.068	0.662	3.005	3.450	1.441	0.0221
28.0	610.0	1.555	0.5853	1.106	0.616	2.362	2.520	1.510	0.0201
44.0	700.0	1.578	0.6207	1.038	0.558	1.859	2.686	1.783	0.0211
81.0	825.0	1.563	0.6972	0.980	0.488	1.445	2.695	2.177	0.0221
121.0	1290.0	1.553	1.0881	0.950	0.320	0.585	2.296	3.628	0.0243
180.0	1550.0	1.577	1.2948	0.898	0.246	0.426	2.649	5.196	0.0280
252.0	1910.0	1.623	1.6129	0.858	0.171	0.291	3.417	8.428	0.0344
324.0	2175.0	1.620	1.7966	0.820	0.136	0.234	4.303	11.654	0.0399
410.0	3007.0	1.525	2.3708	0.728	0.068	0.119	9.703	31.624	0.0643

*Data from Table XV - Run 4

$\sigma_t = 0.2$ min $\sigma_A = 0.005$ $\varepsilon' = 0.202$ $\sigma_{\varepsilon'} = 0.01$ $k_{obs} = [1.571 \pm 0.033] \times 10^{-5} \text{sec}^{-1}$

Average experimental % error in k_{obs} = 2.1%

Average computed % error in k_{obs} = 3.07%

[a] For the definition of these functions see Eq. (73) to (80).

One assumes the pre-exponential factor A' and E_a to be independent of temperature. It can be easily shown that

$$\left(\frac{d\,k_{obs}}{k_{obs}}\right)_{A,E_a} = \frac{E_a}{RT^2}\,dT \quad \text{or} \quad \frac{\Delta k_{obs}}{k_{obs}} = \frac{E_a}{RT^2}\,\Delta T \tag{81}$$

Substituting the values of various parameters in Eq. (81), and, since $\Delta T = 0.1$ K (experimentally observed <u>maximum</u> deviation in T was ± 0.1 K), $E_a = 20.5$ kcal mol^{-1} (experimentally evaluated), R = 1.987 cal deg^{-1} mol^{-1}, T ≈ 300 K we have

$$\frac{\Delta k_{obs}}{k_{obs}} = \frac{20500 \text{ cal mol}^{-1} \times 0.1 \text{ deg}}{1.987 \text{ cal deg}^{-1} \text{ mol}^{-1} \times 300 \times 300 \text{ deg}^2} = 0.012$$

Therefore, for the type of temperature control employed in the present work, i.e., for a maximum deviation of ±0.1° in temperature, a maximum deviation of ±1.2% in k_{obs} would be observed.

Since the temperature control was very crucial, most of the runs were made at a temperature close to the ambient temperature which was close to 25°C. Near ambient temperature, maintenance of constant temperature was found to be easier.

Using the observed maximum deviation in k_{obs} (5%) and $C_{H_3O^+}$ (7%) for the acid solutions of $\utilde{1a}$, an estimated error for the rate constant k'_{obs} (defined by the following equation) is given by the sum of the

$$k'_{obs} = k_{obs} \cdot C_{H_3O^+}$$

relative errors in k_{obs} and $C_{H_3O^+}$ which is 12%, i.e., $\sigma_{k'_{obs}}/k'_{obs} = 12\%$.

It is clear from data on Table VI that the standard deviation in k'_{obs} calculated from the various runs is of the order of 6% which is less than the estimated average maximum error.

While computing the rate constants from solutions of **1a** in H_2O the initial part (20%) of the reaction with the subsequent pH drop (see Figure 3, page 49) has been ignored. For the remaining 80% of the reaction (steady-state region), where a buffering action was observed, the deviation in the average pH was ± 0.05 from the reported values. The rate constants evaluated for these cases in the absence of externally added acid showed an inverse dependence on the initial concentration of the ester **1a**. The rate constant was found to increase from $(23.4 \pm 2.5) \times 10^{-5}$ sec^{-1} to (32.4 ± 10^{-5}) sec^{-1} (i.e. by 27%) when the initial concentration of ester **1a** was reduced from 0.34 mM to 0.25 mM (i.e. by 26%). The inverse dependence of k_{obs} on $(C_{\mathbf{1a}})_o$ in the absence of external acid, could be due to the increased average value of $C_{H_3O^+}$ resulting from the more concentrated solutions of **1a**. Of course, this observation is in agreement with the finding that k_{obs} in the hydrolysis of **1a** is markedly reduced as the pH is lowered by externally added hydrochloric acid. A similar effect was observed in D_2O and therefore in the determination of the solvent isotopic effect, the ratio of the rate constants in H_2O and D_2O were determined from solutions with identical initial concentrations of ester **1a**. Thus, inverse dependence of k_{obs} on $(C_{\mathbf{1a}})_o$ was also noted in D_2O (see Tables XXI and XXII).

An attempt was made for correcting the curvature observed (noted in the initial period of the reaction in the absence of external acid) in the plot of the rate shown in Figure 3 (page 49). The following function ϕ' was calculated at different intervals of time from the experi-

$$\phi' = \{- \log_e (C)_t + \log_e (C)_o\} C_{H_3O^+}$$

mentally-measured absorbance and pH values using Eq. (42) on page 90. A plot of the function ϕ' versus time t was found to be linear without curvature in the function ϕ'. This explains, at least qualitatively, that the initial curvature in the function $-\log_e(C)_t$ in Figure 3 probably arises from the drop in pH observed in the same time frame. However, the slope of the curve (ϕ' versus t) was found to be 2.15 x 10^{-8} mol L^{-1} sec^{-1}. Comparing Eqs. (22), (24), and (25) (see page 86), this slope should give the value of k'_{obs}. However, the value found for k'_{obs} (evaluated as described above) was 1.8 times larger (k'_{obs} determined experimentally was 1.2 ± 0.1 x 10^{-8} mol L^{-1} sec^{-1}) than k'_{obs} as evaluated from solutions of $\underset{\sim}{1a}$ in aqueous hydrochloric acid. The linearity of the function ϕ' with time t at least qualitatively explains the effect of the pH (drop in pH) on the initial curvature (Figure 3). Nevertheless, the discrepancy in the slope and the lack of quantitative agreement between the calculated and found k'_{obs} values could also be the result of equipment deficiencies. Since the glass electrode used to measure the pH requires a finite period of 2-3 minutes for equilibration, it is quite possible that the pH values in the initial period may not represent true instantaneous values of ($C_{H_3O^+}$).

Errors in Activation Parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$

Returning to the Arrhenius Eq.

$$k_{obs} = A' e^{-E_a/RT}$$

the standard deviation in E_a could be evaluated from the Eq. (82) given by Binsch.[19]

$$\left(\frac{\sigma_{E_a}}{E_a}\right)^2 = \frac{2T^2}{(\Delta T)^2}\left(\frac{\sigma_T}{T}\right)^2 + 2[\Delta \ln k'_{obs}]^{-2} (\sigma_{k'_{obs}}/k'_{obs})^2 \qquad (82)$$

Substituting the values of various parameters from Table XXX in Eq. (82) using the following values for specific terms, we have:

$T = T_{average} = 300$ K

ΔT = range of temperature = 15 K

σ_T = standard deviation in T = 0.1 K

$\Delta \ln k'_{obs}$ = range of $\ln k'_{obs}$ = 18.98 - 17.24 = 1.74

$\frac{\sigma_{k'_{obs}}}{k'_{obs}}$ = 0.12 (estimated error)

However, σ_{E_a}/E_a could be evaluated from Eq. (82):

$$(\sigma_{E_a}/E_a)^2 = \frac{2 \times (300)^2}{(15)^2}\left(\frac{0.1}{300}\right)^2 + \frac{2}{(1.74)^2}(0.12)^2$$

In other words, the following ratio persists:

$$\sigma_{E_a}/E_a = 0.0975$$

[This corresponds to an error of 9.75% (average deviation in E_a)]. Since $\Delta H^{\ddagger} = E_a - RT$ and $\sigma_{E_a} \gg \sigma_T$, we have:

$$\sigma_{E_a}/E_a \approx \sigma_{\Delta H^{\ddagger}}/\Delta H^{\ddagger} \approx 0.0975$$

Since $\Delta H^{\ddagger}$ was evaluated as 19.9 kcal/mol, $\sigma_{\Delta H^{\ddagger}}$ is found to be 19.9 x 0.0975 kcal/mol (or 1.94 kcal/mol), or incorporating the average deviation, $\Delta H^{\ddagger} = 20 \pm 2$ kcal/mol. For the evaluation of error in $\Delta S^{\ddagger}$, extreme values of ln A' were evaluated numerically by substituting the extreme values of E_a (18.5 kcal/mol and 22.5 kcal/mol) using the following format for the Arrhenius Eq. (60):

$$\log_e k'_{obs} = \log_e A' - E_a/RT \tag{60}$$

Solving for $\log_e A'$ using the values for k'_{obs} from Table XXX [it is assumed for the purpose of error evaluation in A' that the change in $\log_e k'_{obs}$ arising from a change of 10% in E_a at constant temperature is negligible compared to change produced in $\log_e A'$ in Eq. (60)], the difference between the extreme values of $\log_e A'$ was found to be $\Delta\log_e A' = 3.42$. This should be considered as the maximum error in $\log_e A'$ as a consequence of an error of 10% in E_a. The corresponding error in $\Delta S^{\ddagger}$ could be computed from Eq. (65):

$$\Delta S^{\ddagger} = R(\log_e A' - \log_e \frac{kT}{h} - 1) \tag{65}$$

Assuming that the total error in A' is reflected as error in ΔS, then

$$\Delta\Delta S^{\ddagger} = R(\Delta\log_e A') = 1.987 \times 3.42 = 6.8 \text{ eu}$$

Thus, $\Delta S^{\ddagger}$ previously evaluated as -44.2 eu (n = 2) and -52.2 eu (n = 3) could be better represented as $\Delta S^{\ddagger} = -44 \pm 7$ eu (n = 2) or -52 ± 7 eu (n = 3) incorporating the evaluated maximum error factors.

Raman Spectral Analysis

Laser Raman spectra of ester **1a** in the liquid state (neat) was recorded, and indicated a C=O stretching frequency at 1660 cm^{-1}. Raman spectra in the vicinity of the C=O stretching frequency was scanned very carefully with suspensions of 1a in both D_2O and in D_2O + HCl. Suspensions of ester 1a used for recording the Raman spectra had the following compositions: (1) 4 μL of 1a in 5 mL of D_2O and (2) 4 μL of 1a in a mixture containing 5 mL of D_2O and 0.05 mL of 0.1 N HCl. Spectra for blank (of a solution) of HCl- 0.05 mL of 0.1 N HCl + 5 mL of D_2O, and D_2O without 1a were also recorded for comparison purposes. Each spectral region was scanned at least three times for consistency and results are recorded in Table VII.

^{31}P NMR Spectral Data

Freshly distilled samples of the esters, 1a, 1b, 1c and 3 were transferred into a 12 mm NMR tube with the help of a microsyringe and the esters were dissolved in a measured volume of an appropriate solvent described in Table IV. ^{31}P NMR spectra were obtained in the FT mode by pulsing for a length of time depending upon the concentrations of ^{31}P species which were examined in solution. In those cases where D_2O was part of the solvent, the ^{2}D lock was used. In all other cases, the ^{1}H lock was used to obtain the spectra. The spectra were scanned visually on the oscilloscope over a region of ±5000 Hz from 85% H_3PO_4 used as an external reference. The relevant portions of the spectra were recorded (see Plates I to XI). A sealed 1-mm capillary tube containing 85% H_3PO_4 was introduced into the 12-mm NMR tube to record the reference signal. In those cases where the pulsing period was high (the number of acquisition > 200) and in cases where signals belonging to the spectra overlapped with those of 85% H_3PO_4, the reference signals were separately recorded and added to the spectra. The probe temperature was maintained at 36 ± 1°C while the spectra were recorded. Pulse parameters used for obtaining the ^{31}P NMR spectra were: delay time between pulses = 15 sec, and pulse width = 11.8 μsec. It was assumed that duration of 15 sec would be long enough to permit relaxation of ^{31}P nuclei, so that the integrated areas under the ^{31}P NMR signals could be a measure of the relative concentrations. Even with a delay time of 40 sec used in one of the experiments performed as a check, the area ratios under the ^{31}P NMR signals were not altered. The areas under the signals were obtained by conventional methods, i.e., by electronic integration, planimeter measurement of areas, or by weighing. The agreement was within ±3% in the areas computed by different methods. For obtaining the broad band ^{1}H decoupled ^{31}P NMR spectra in solutions of esters 1a and 3 [see Plates VII(A) and VII(B)], the offset frequency was set at 45689 Hz ± 500 Hz which corresponds to about δ 6.7 for decoupling both H-P and P-O-C-H protons. Authentic samples of $HP(O)(OEt)_2$ (3) and ester 1a were employed as model systems for ^{31}P NMR studies of the hydrolysis of ester 1a in D_2O. Signals corresponding to the substituents of H or alkyl groups of the ester portion were easily discernable (see Plates II, III, IV, V, VI and VII). Thus signals from products and the deuterated analogs of model systems 3[29,36], 45[36,85] and 52[85] were detected.

PLATE I. ^{31}P NMR FT Spectrum of Diethyl Benzoylphosphonate (**1a**).

solvent.....dioxane
S.F.....40.54 MHz
ACQ.....40
D_5.....15 sec
Lock.....^{1}H

concentration.....*ca*. 0.2 M
S.O.....49001 Hz
P_2.....11.8 μsec
S.W.....1000 Hz

PLATE I

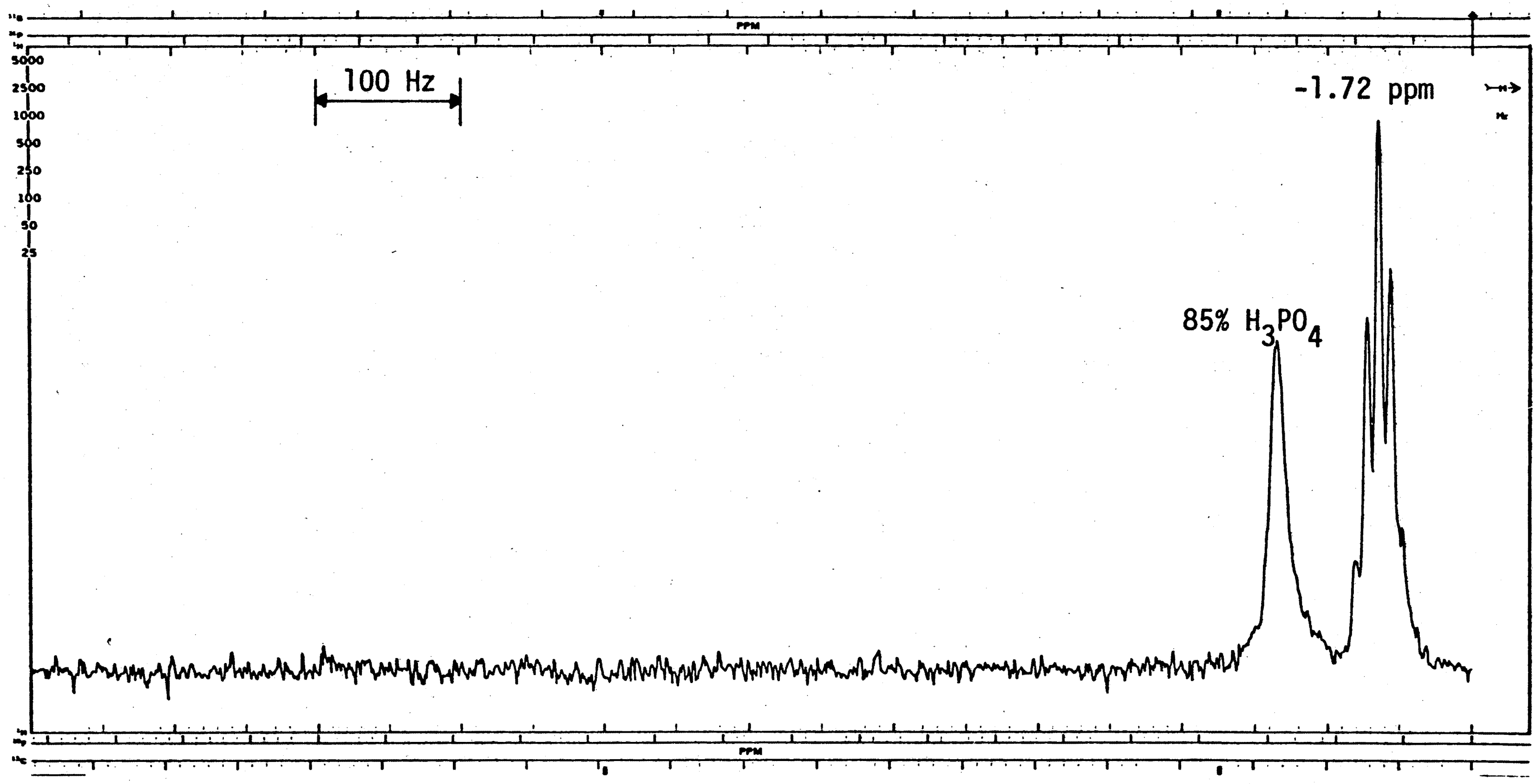


PLATE II. ^{31}P NMR FT Spectra of a Solution of Diethyl Benzoylphosphonate (1a) in 1:1 v/v Dioxane + HCl (0.9 N) + D_2O (16%) at Different Intervals of Time (from t_o + 0.75 hr to t_o + 29 hr).

(A) $(C_{1a})_o$ = 0.0235 M, t_o + 0.75 hr + 200 ACQ
(60 min of signal accumulation)

(B) $(C_{1a})_o$ = 0.023 M, t_o + 16.75 hr + 200 ACQ
(60 min of signal accumulation)

(C) $(C_{1a})_o$ = 0.07 M, t_o + 29 hr + 160 ACQ
(48 min of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^{1}J_{PH(or\ D)}$ in Hz

a, R = R' = Et (1a), - 1.21, 0

b, HP(O)(OEt)(OH) (45), 6.5, 680

c, $HP(O)(OH)_2$ (52), 4.0, 680

d, R = Et, R' = H (43a), - 2.3, 0

e, R = R' = H (51a), - 2.9, 0

PLATE II

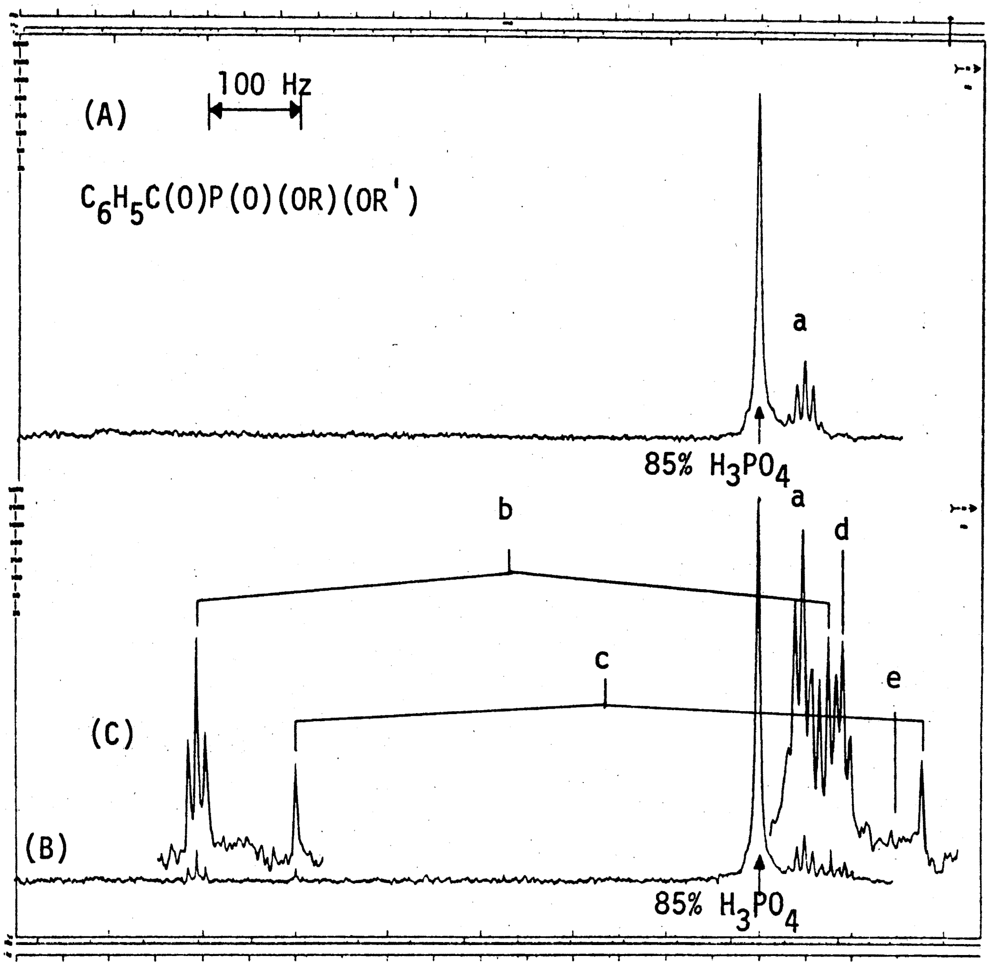


PLATE III. ^{31}P NMR FT Spectra of a Solution of Diethyl Benzoylphosphonate (1a) in 1:1 v/v Dioxane + HCl (0.9 N) + D_2O (16%) at Different Intervals of Time (from t_o + 143 hr to t_o + 1439.5 hr).

(A) $(C_{1a})_o$ = 0.023 M, t_o + 143.25 hr + 200 ACQ (60 min of signal accumulation)

(B) $(C_{1a})_o$ = 0.023 M, t_o + 359 hr + 200 ACQ (60 min of signal accumulation)

(C) $(C_{1a})_o$ = 0.23 M, t_o + 1439.5 hr + 200 ACQ (60 min of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^1J_{PH(or\ D)}$ in Hz

a, HP(O)(OEt)(OH) (45), 6.5, 680

b, $HP(O)(OH)_2$ (52), 4.0, 680

c, $DP(O)(OD)_2$ (52D), 3.7, 100

d, R = Et, R' = H (43a), - 2.3, 0

e, R = R' = H (51a), - 2.9, 0

PLATE III

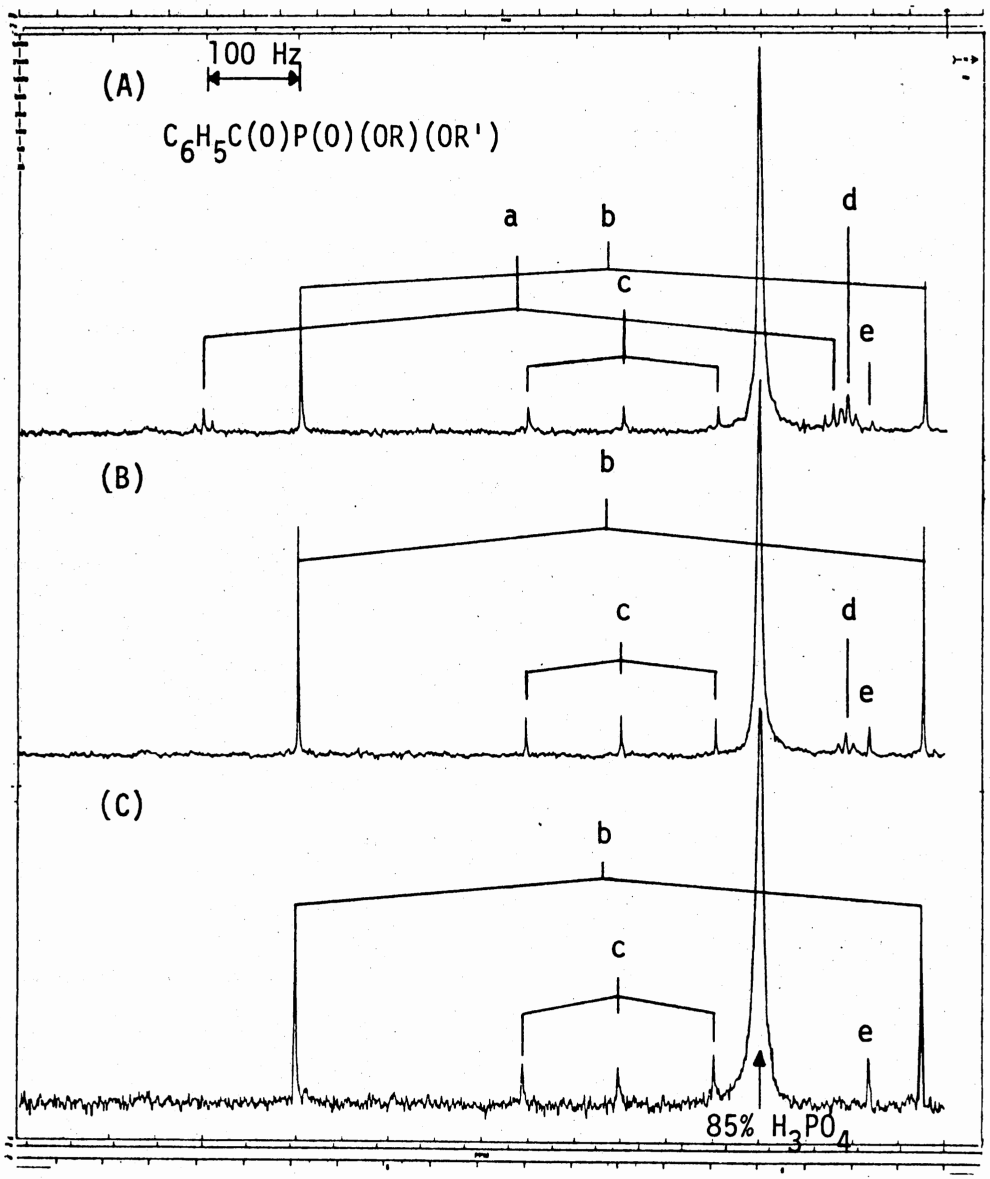


PLATE IV. ^{31}P NMR FT Spectrum of Diethyl Hydrogenphosphonate (3).

Solvent.....D_2O	Concentration.....*ca*. 0.2 M
S.F.....40.5 MHz	S.O.....49001 Hz
ACQ.....40	P_2.....11.8 μsec
D_5.....15 sec	S.W.....2000 Hz
Lock.....^{2}D	

PLATE IV

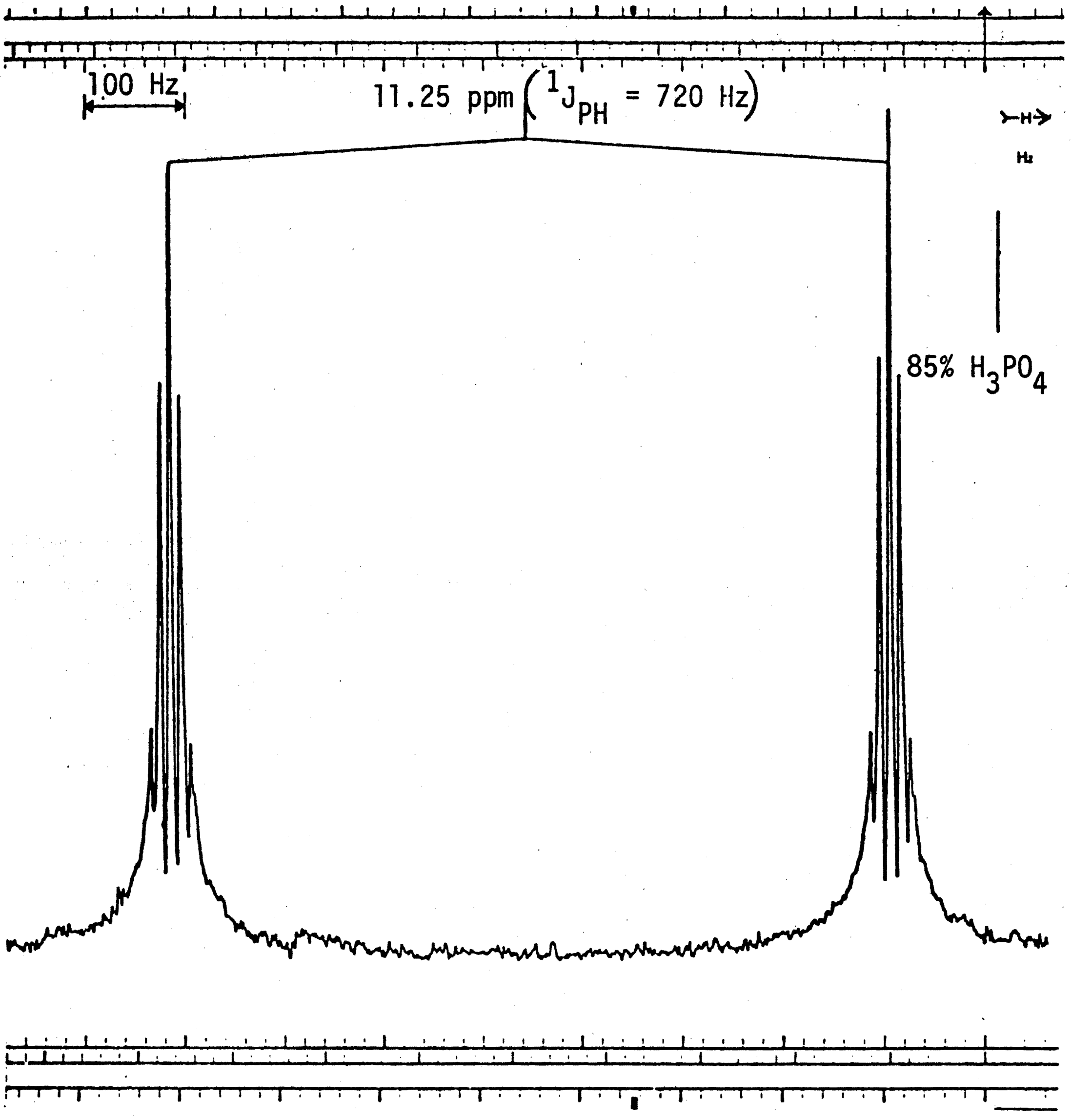


PLATE V. ^{31}P NMR FT Spectra of a Solution of Diethyl Hydrogenphosphonate (**3**) in 1:1 v/v Dioxane + HCl (0.9 N) + D_2O (16%) at Different Intervals of Time.

(A) $(C_{\mathbf{3}})_o$ = *ca.* 0.2 M, t_o + 5 min + 140 ACQ (40 min of signal accumulation)

(B) $(C_{\mathbf{3}})_o$ = *ca.* 0.2 M, t_o + 360 hr + 80 ACQ (23 min of signal accumulation).

Symbolism

letter for signal, cpd, ppm, $^1J_{PH(or\ D)}$ in Hz

a, $HP(O)(OEt)_2$ (**3**), 9.97, 710

b, HP(O)(OEt)(OH) (**45**), 6.49, 680

c, $HP(O)(OH)_2$ (**52**), 4.0, 680

d, $DP(O)(OD)_2$ (**52D**), 3.7, 100

PLATE V

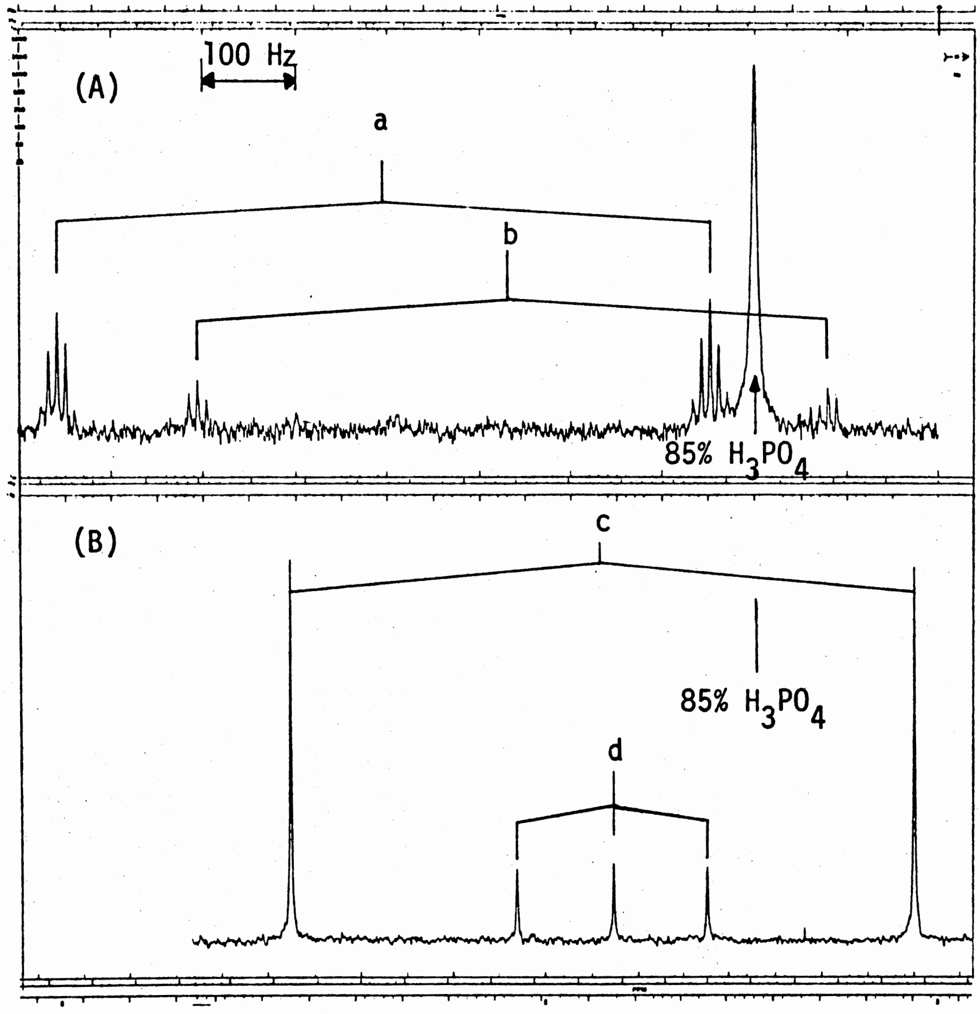


PLATE VI. ^{31}P NMR FT Spectra of a Partially Hydrolyzed Solution of Diethyl Hydrogenphosphonate (3).

(A) solvent - 1:1 v/v dioxane + HCl (0.9 N) + D_2O (16%), *ca.* $(C_3)_o$ = 0.45 mM, spectrum observed after t_o + 4 hr and 64 ACQ (18 min of signal accumulation)

(B) solvent - aqueous hydrochloric acid (0.106 mM), *ca.* $(C_3)_o$ = 0.45 mM, spectrum observed after t_o + 28 hr and 64 ACQ (18 min of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^{1}J_{PH(or\ D)}$ in Hz

a, $HP(O)(OEt)_2$ (3), 10.15, 710

b, $HP(O)(OEt)(OH)$ (45), 6.59, 680

c, $DP(O)(OEt)_2$ (3D), 9.32, 109

d, $DP(O)(OEt)(OD)$ (45D), 6.32, 102

a', $HP(O)(OEt)_2$ (3), 11.25, 720

b', $HP(O)(OEt)(OH)$ (45), 6.74, 660

c', $HP(O)(OH)_2$ (52), 4.25, 665

PLATE VI

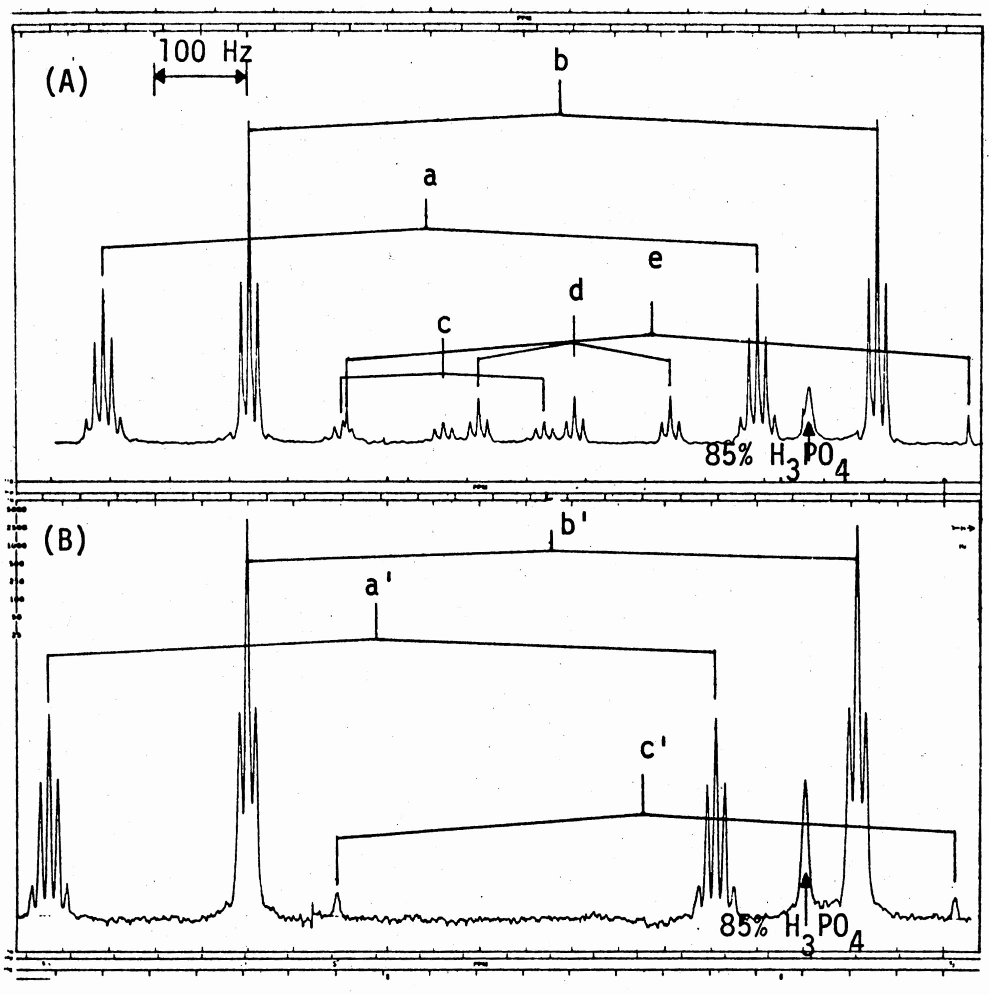


PLATE VII. ^{31}P NMR FT Spectra (Proton Decoupled of a Partially Hydrolyzed Solution of Diethyl Hydrogenphosphonate (3) and of a Partially Hydrolyzed Solution of Diethyl Benzoylphosphonate (1a).

solvent - 1:1 v/v dioxane + HCl (0.9 N) + D_2O (16%)

(A) solution of (3), $(C_3)_o$ = *ca.* 0.45 M, spectrum observed (prior to decoupling) after t_o + 4 hr and 64 ACQ (18 min of signal accumulation)

(B) solution of (3), $(C_3)_o$ = *ca.* 0.45 M, broad 'H decoupled spectrum observed after t_o + 4.33 hr and 48 ACQ (12 min of signal accumulation)

(C) solution of (1a), $(C_{1a})_o$ = *ca.* 0.07 M, broad 'H decoupled spectrum after t_o + 30 hr and 160 ACQ (45 min of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^1J_{PH(or\ D)}$ in Hz
a, a', a", $HP(O)(OEt)_2$ (3), 10.15, 710
b, b', b", HP(O)(OEt)(OH) (45), 6.59, 680
c, c', $DP(O)(OEt)_2$ (3D), 9.32, 109
d, d', d", DP(O)(OEt)(OD) (45D), 6.32, 102
e, e', e", $HP(O)(OH)_2$ (52), 3.97, 670
f, intermediate hydrate of 1a, 43a, or 51a (?) 17.4, 0
g, intermediate hydrate of 1a, 43a, or 51a (?) 16.30, 0
h, intermediate hydrate of 1a, 43a, or 51a (?), 0.0, 0
i, PhC(O)P(O)(OEt)(OH) (43a), - 1.34, 0
j, $PhC(O)P(O)(OH)_2$ (51a), - 2.35, 0

PLATE VII

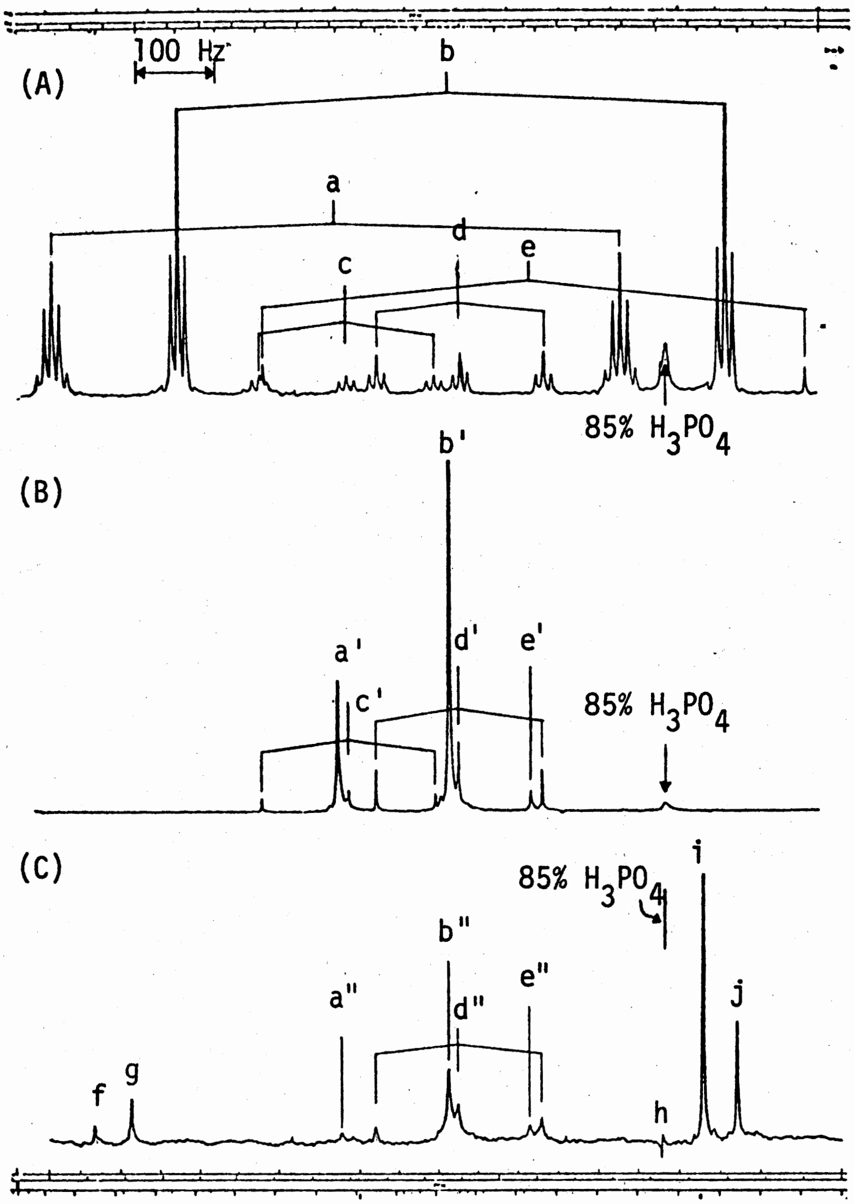


PLATE VIII. ^{31}P NMR FT Spectra of Diethyl Benzoylphosphonate (**1a**) in 1.06 mM Aqueous HCl at Different Intervals of Time (From t_o + 5 min to t_o + 52 hr $(C_{\mathbf{1a}})_o$ = 17 mg of **1a** in 3 mL of HCl).

(A) t_o + 15 min + 3500 ACQ (15 hr of signal accumulation)

(B) t_o + 27.5 hr (*ca.* 2 half lives) + 3500 ACQ (15 hr of signal accumulation)

(C) t_o + 52 hr (*ca.* 4 half lives) + 3500 ACQ (15 hr of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^1J_{PH(or\ DP)}$ in Hz

a, a', a", HP(O)(Et)$_2$ (**3**), 11.3, 720

b, b', b", hydrated carbonyl intermediate (**40a**), 17.9, 0

c, c', c", hydrated phosphonyl intermediate (**39a**), - 0.30, 0

d, HP(O)(OEt)(OH) (**45**), 6.6, 660

PLATE VIII

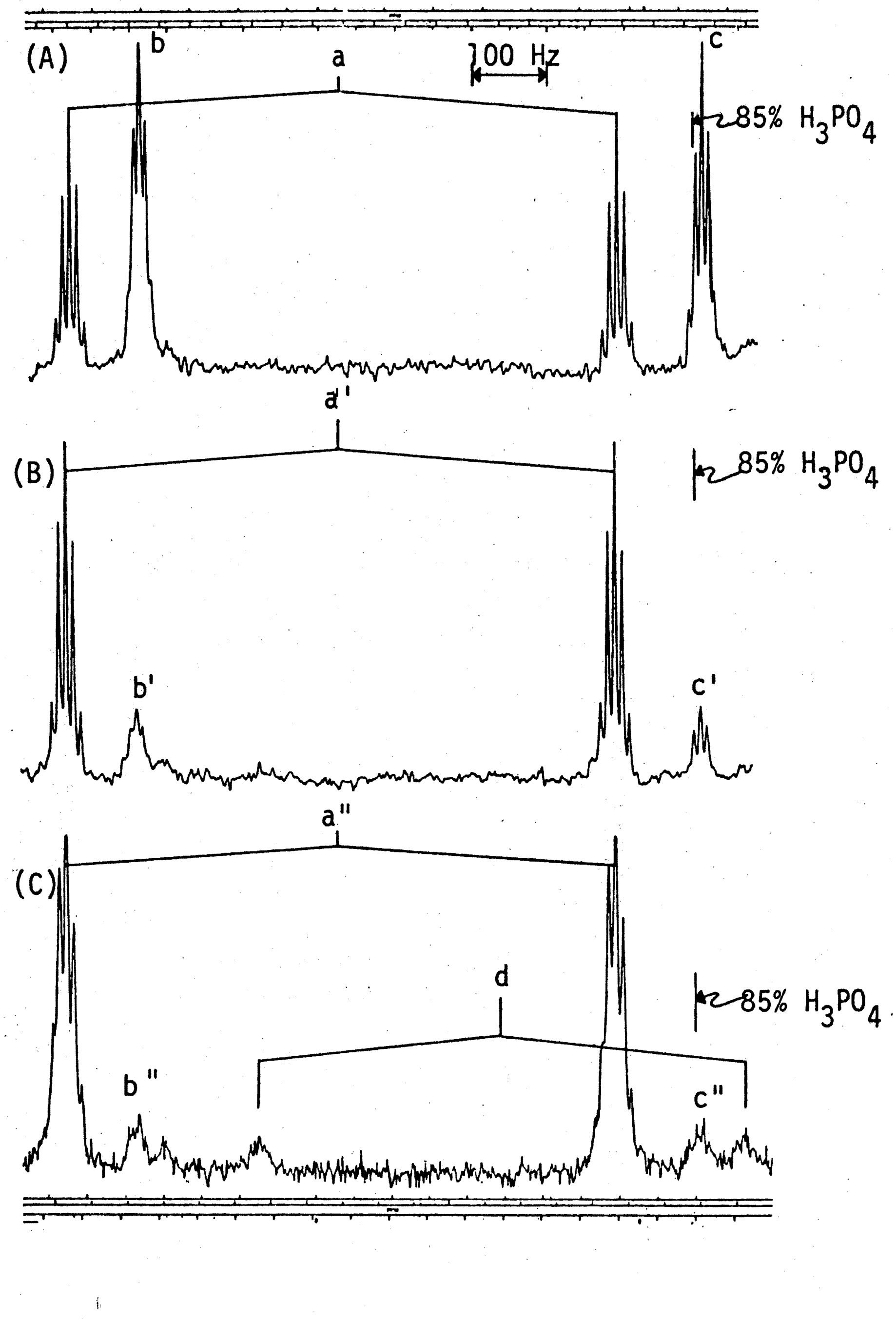


PLATE IX. ^{31}P NMR FT Spectra of an Aqueous Suspension of Diethyl Benzoylphosphonate (**1a**) at t_o + 5 min and Effects of Addition of Excess of Esters **1a** and **3**.

(A) $(C_{\mathbf{1a}})_o$ = 17 mg of **1a** in 3 mL of H_2O, t_o + 5 min + 216 ACQ (*ca.* 60 min of signal accumulation)

(B) spectrum observed after addition of large excess (*ca.* 100 mg) of the parent ester **1a** to the above suspension described under (A) at t_o + 65 min followed by 36 ACQ (10 min of signal accumulation)

(C) spectrum observed after addition of large excess (*ca.* 300 mg) of **3** to the above suspension described under (B) at t_o + 75 min followed by 36 ACQ (10 min of signal accumulation)

Symbolism

letter for signal, cpd, ppm, $^1J_{PH(or\ D)}$ in Hz

a, a', a", hydrated carbonyl intermediate (**40a**), 17.9, 0

b, b', b", hydrated phosphonyl intermediate (**39a**), - 0.30, 0

c, c', carbonyl form of ester (**1a**), - 1.9, 0

d, HP(O)(OEt)$_2$ (**3**), 11.3, 720

PLATE IX

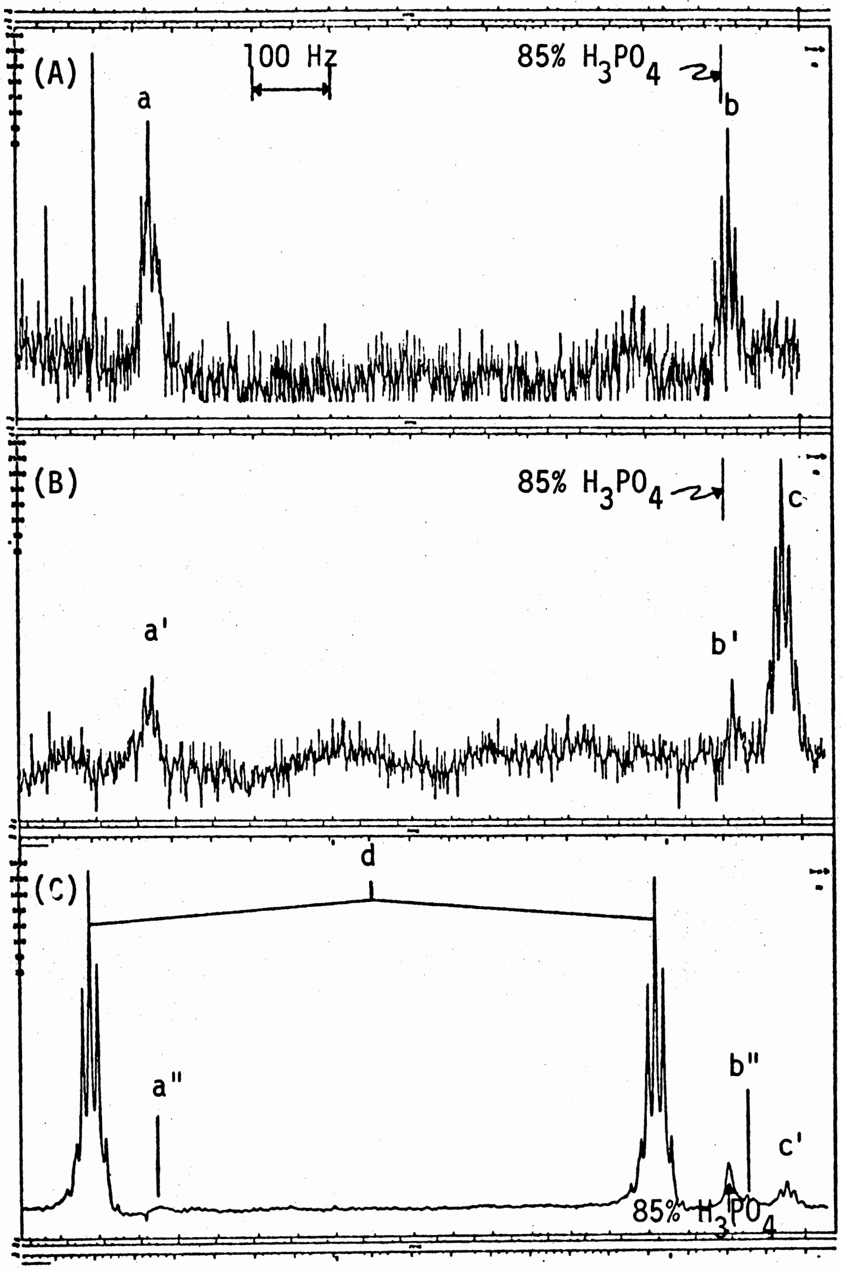


PLATE X. ^{31}P NMR FT Spectra of Diethyl *p*-Chlorobenzoylphosphonate (**1b**) in Dioxane and Aqueous HCl.

(A) solvent-dioxane, $(C_{1b})_o$ = *ca.* 0.2 M, t_o + 5 min + 64 ACQ (18 min of signal accumulation

(B) solvent-aqueous HCL (0.1 mM), $(C_{1b})_o$ = *ca.* 17 mg of **1b** suspended in 3 mL of HCl, t_o + 5 min + 360 ACQ (90 min of signal accumulation)

(C) spectrum of the suspension described in (B) after 3200 ACQ (*ca.* 14 hr of signal accumulation)

Symbolism

letter for signal, cpd, ppm

a, a', a", carbonyl form of ester, **1b**, - 1.92

b, b', hydrated carbonyl intermediate from ester **1b** (**40b**)(?), 17.56

c, c', hydrated phosphonyl intermediate from ester **1b** (**39b**)(?), - 0.65

d, $HP(O)(OEt)_2$ (**3**), 11.35 $\left({}^{1}J_{PH} = 720 \text{ Hz}\right)$

PLATE X

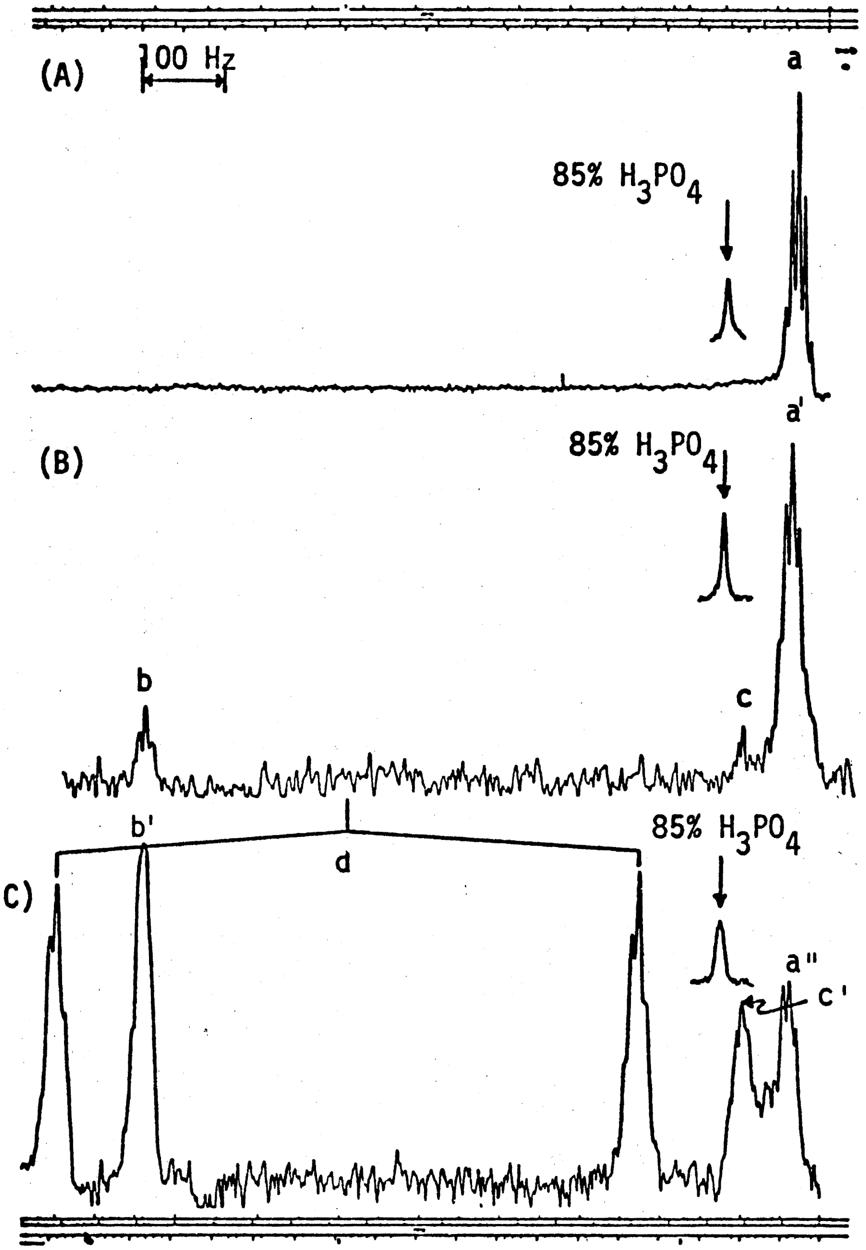


PLATE XI. ^{31}P NMR FT Spectra of Diethyl *p*-Toluoylphosphonate (1c) in Dioxane and Aqueous HCl.

(A) solvent-dioxane, $(C_{1c})_o$ = *ca.* 0.3 M, t_o + 5 min + 20 ACQ (6 min of signal accumulation)

(B) solvent-aqueous HCl (0.1 mM), $(C_{1c})_o$ = *ca.* 17 mg of 1c suspended in 3 mL of HCl, t_o + 5 min + 3200 ACQ (*ca.* 14 hr of signal accumulation)

Symbolism

letter for signal, cpd, ppm

a, a', carbonyl form of ester 1c, - 1.40

b, $HP(O)(OEt)_2$ (3), 11.53 [$^1J_{PH}$ = 730 Hz]

c, hydrated carbonyl intermediate from ester 1c (40c)(?), 18.12

d, hydrated phosphonyl intermediate from ester 1c (39c)(?), 0.0

PLATE XI

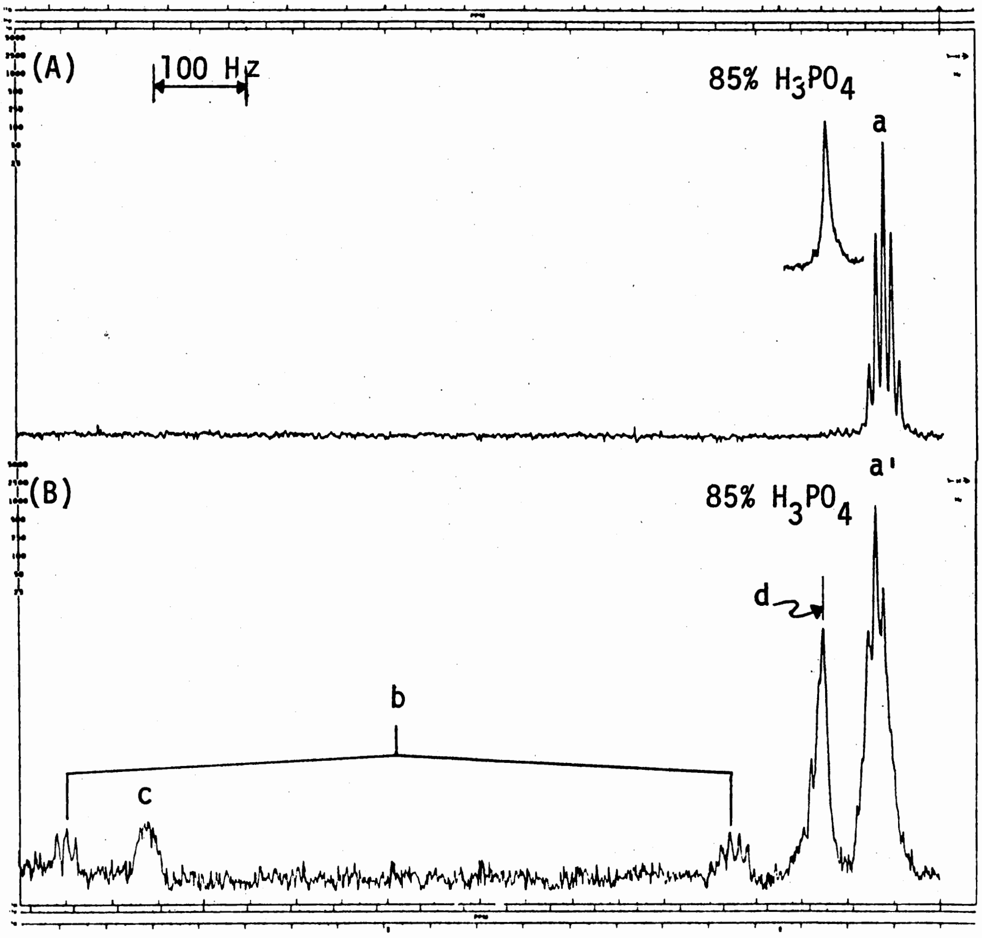


PLATE XII. ^{1}H NMR Spectrum of Diethyl *p*-Toluoylphosphonate (**1c**).

Solvent.....$DCCl_3$
F.B.....2.0 Hz
S.W.....1000 Hz
S.O.....87091 Hz
Lock.....^{1}H

S.F.....100.1 MHz
R.F.....60 dB
S.T.....250 sec
S.A.....3.2

PLATE XII

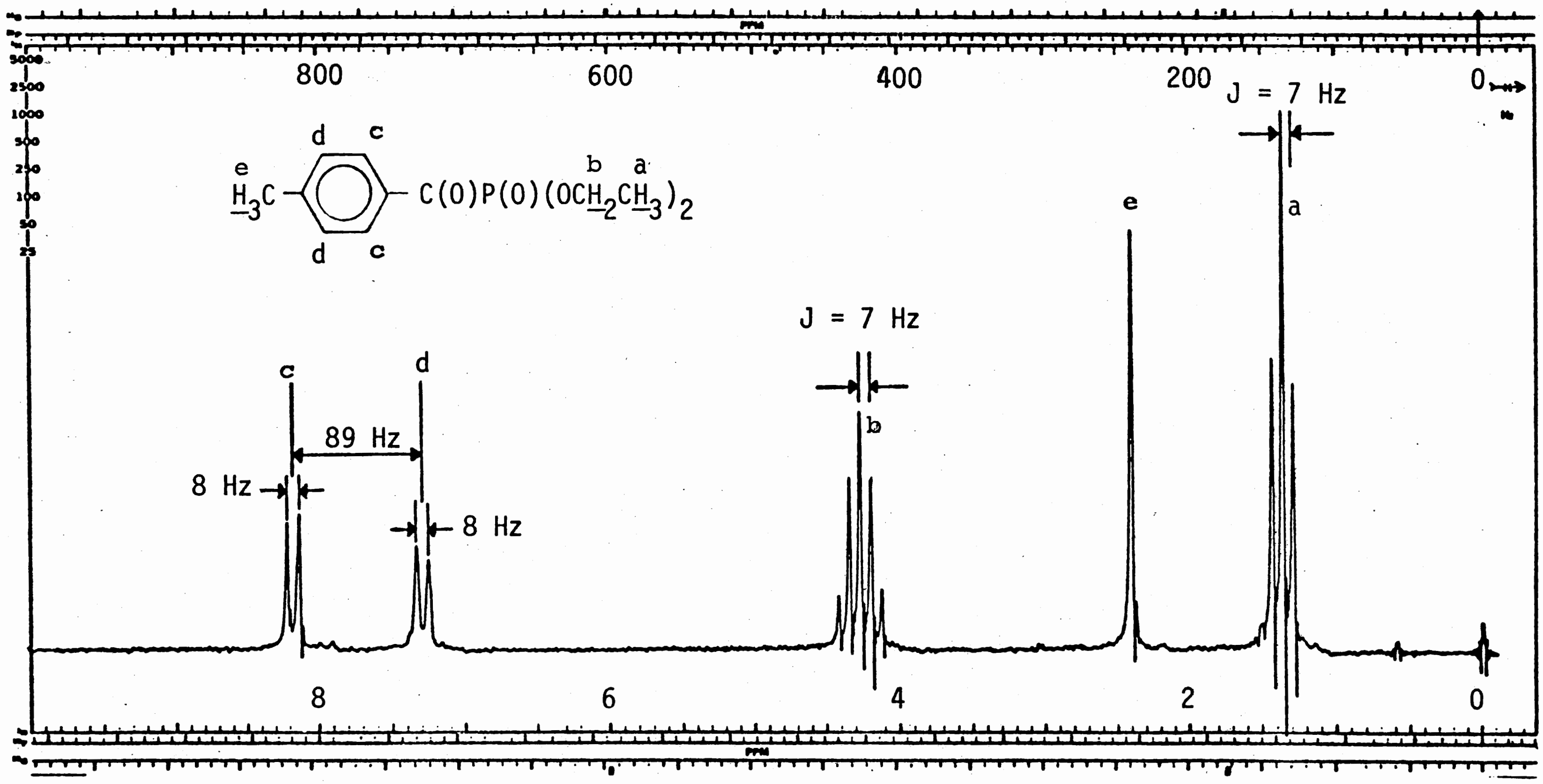
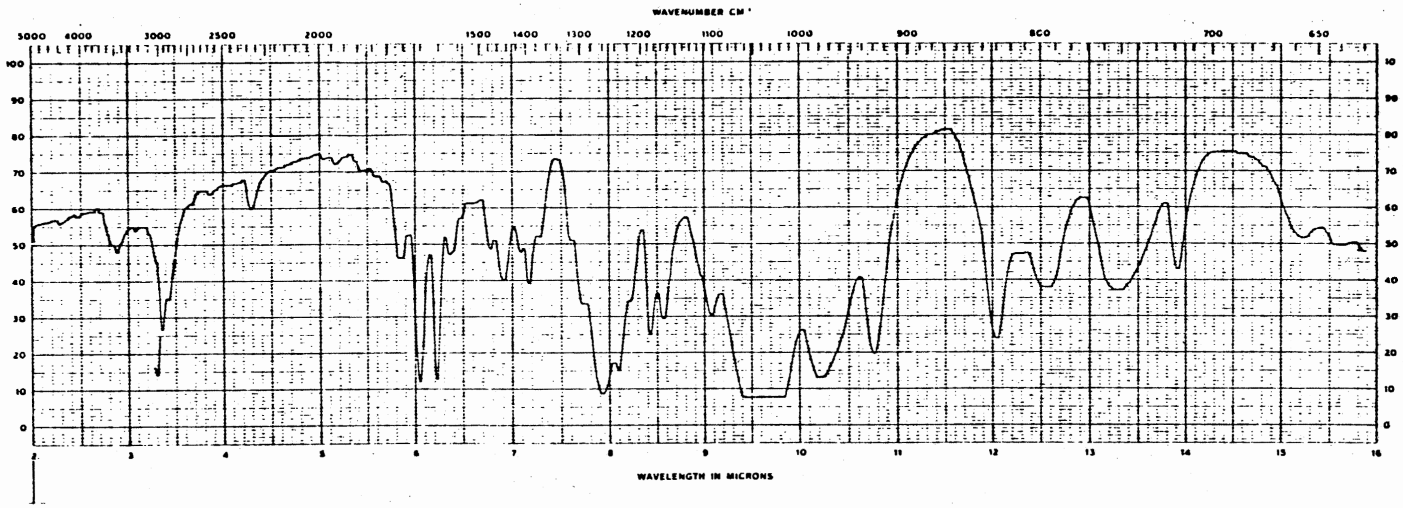

800
600
400
200
0
J = 7 Hz
e
b
a
H$_3$C
C(O)P(O)(OCH$_2$CH$_3$)$_2$
d
c
e
a
J = 7 Hz
b
c
d
89 Hz
8 Hz
8 Hz
8
6
4
2
0
PPM
PPM

PLATE XIII. IR Spectrum of Diethyl p-Toluoylphosphonate (1c), Film on NaCl Plates.

PLATE XIII


WAVENUMBER CM⁻¹
5000
4000
3000
2500
2000
1500
1400
1300
1200
1100
1000
900
800
700
650
100
90
80
70
60
50
40
30
20
10
0
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
WAVELENGTH IN MICRONS

BIBLIOGRAPHY

1. Ackermann, B., Jordan, T. A., Eddy, C. R., and Swern, D., *J. Am. Chem. Soc.*, **78**, 4444 (1956).

2. Andreae, S. and Jugelt, W., *Z. Chem.*, **13**, 136 (1973).

3. Arbuzov, B. A., Vinogradova, V. S., Polezhaeva, N. A., Shamsutdinova, A. K., *Izv. Akad. Nauk. SSSR. Otd. Khim.*, 675 (1963); *Chem. Abstr.*, **59**, 11551 (1963).

4. Asano, S., Kitahara, T., Ogawa, T., and Matsui, M., *Agr. Biol. Chem.*, **37**, 1193 (1973).

5. Augustine, R. L. and Caputo, J. A., *Org. Syn.*, **45**, 80 (1965).

6. Bell, R. P., "The Protons in Chemistry," 2nd ed., Cornell University Press, Ithaca, New York, 1973, pp. 183-190.

7. Bell, R. P. and Critchlow, J. E., *Proc. Roy. Soc.*, **A325**, 35, (1971).

8. Bell, R. P., Millington, J. P., and Pink, J. M., *Proc. Roy. Soc.*, **A303**, 1 (1968).

9. Belski, V. E., Motygullin, G. Z., *Izv. Akad. Nauk. SSSR, Ser. Khim.*, [11], 2551 (1967); *Chem. Abstr.*, **68**, 108353k (1968).

10. Belski, V. E., Motygullin, G. Z., Eliseenkov, V. N., and Pudovik, A. N., *Izv. Akad. Nauk. SSSR. Ser. Khim.*, [6], 1297 (1969); *Chem. Abstr.*, **71**, 80416u (1969).

11. Benson, S. W., "The Foundation of Chemical Kinetics," McGraw-Hill, New York, 1960, pp. 50-53.

12. Berlin, K. D. and Burpo, D. M., *J. Org. Chem.*, **31**, 1304 (1966).

13. Berlin, K. D., Claunch, R. T., Gaudy, E. T., *J. Org. Chem.*, **33**, 3090 (1968).

14. Berlin, K. D., Hellwege, D. M., and Nagabhushanam, M., *J. Org. Chem.*, **30**, 1265 (1965).

15. Berlin, K. D., Roy, N. K., Claunch, R. T., and Bude, D., *J. Am. Chem. Soc.*, **90**, 4494 (1968).

16. Berlin, K. D., Rulison, D. S., and Arther, P., Anal. Chem., 41, 1554 (1969).

17. Berlin, K. D. and Taylor, H. A., J. Am. Chem. Soc., 86, 3862 (1964).

18. Bevington, P. R., "Data Reduction and Error Analysis for the Physical Sciences," McGraw-Hill, Inc., New York, 1969, pp. 56-65.

19. Binch, G., "Dynamic Nuclear Magnetic Resonance Spectroscopy," L. M. Jackman, and F. A. Cotton (Eds.), Academic Press, New York, 1975, Ch. 3.

20. Blackburn, G. M. and Brown, M. J., J. Am. Chem. Soc., 91, 525 (1969).

21. Bunton, C. A., Shiner, Jr., V. J., J. Am. Chem. Soc., 83, 3214 (1961).

22. Burger, I. L. and Wagner, R. M., J. Chem. Eng. Data, 3, 310 (1958).

23. Callis, C. F., Van Wazer, J. R., Schoolery, J. N., and Anderson, W. A., J. Am. Chem. Soc., 79, 2719 (1957).

24. Chantrenne, H., Nature, 160, 603 (1947).

25. Clark, P. E., Ph.D. Thesis, Oklahoma State University, May, 1972.

26. Clark, P. E., Berlin, K. D., Mosbo, J., and Verkade, J. G., Phosphorus, 2, 265 (1973).

27. Claunch, R. T., Ph.D. Thesis, Oklahoma State University, July, 1967.

28. Covington, A. K., Paabo, M., Robinson, R. A., and Bates, R. G., Anal. Chem., 40, 700 (1968).

29. Crutchfield, M. M., Dungan, C. H., Van Wazer, J. R., "Topics in Phosphorus Chemistry," M. Garyson, E. J. Griffith (Eds.), Interscience New York, 1966, V. 5, p. 11.

30. Edwards, J. O., Greene, E. F., and Ross, J., J. Chem. Ed., 45, 381 (1968).

31. Eigen, M., Disc. Faraday Soc., 39, 7 (1965).

32. Emsley, J. and Hall, D., "The Chemistry of Phosphorus", Wiley, New York, N.Y., 1976, p. 106.

33. Eyring, H., J. Chem. Phys., 3, 107 (1935), ibid., 492 (1935).

34. Farrar, T. C., and Becker, E. D., "Pulse and Fourier Transform NMR Introduction to Theory and Methods," Academic Press, New York, 1971.

35. Feinstein, R. N., *J. Org. Chem.*, **24**, 1172 (1959).

36. Fluck, E. and Binder, H., *Z. Naturforsch., Teil B*, **22**, 805 (1967); *Chem. Abstr.*, **68**, 25325b (1968).

37. Francina, A., Lamotte, A., and Merlin, J. C., *C. R. Acad. Sci., Paris, Ser. C.*, **266**, 1050 (1968); *Chem. Abstr.* **69**, 58642b (1968).

38. Froalich, P. M., Seminar Lecture at Chemistry Department, Oklahoma State University, March 9, 1978.

39. Gakis, N., Heimgartner, H., and Schmid, H., *Helv. Chim. Acta.*, **58**, 748 (1975).

40. Gareev, R. D., Pudovik, A. N., Samitov, Yu. Yu., *Khim. Elementoorg. Seodin.* 135, (1976); *Chem. Abstr.*, **86**, 29308t (1977).

41. Gillespie, P., Ramirez, F., Ugi, I., and Marquarding, D., *Angew. Chem. Int. Ed.*, **12**, 91 (1973).

42. Glonek, T., *J. Am. Chem. Soc.*, **98**, 7090 (1976).

43. Gordon, M., Notaro, V. A., and Griffin, G. E., *J. Am. Chem. Soc.*, **86**, 1898 (1964).

44. Gould, E. S., "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, 1959, p. 379.

45. Halmann, M., Vofsi, D., and Yanai, S., *J. Chem. Soc., Perkin Trans.* **2**, 1210 (1976).

46. Hammett, L. P., "Physical Organic Chemistry," 2nd ed., McGraw Hill, New York, New York, 1970, pp. 316-345.

47. Hart, P. A., *Abstr. 170th ACS Meeting*, Chicago, Illinois; August, 1975; ORGN-118.

48. Hellwege, D. M., Private Communication.

49. Hirsch, J. A., "Concepts in Theoretical Organic Chemistry," Allyn and Bacon, Inc., Boston, 1975, pp. 159-160.

50. Hosoya, H. and Nagakura, S., *Spectrochim. Acta*, **17**, 324 (1961).

51. Hudson, H. R. and Roberts, J. C., *J. Chem. Soc., Perkin Trans.*, **2**, 1575 (1974).

52. Hutchinson, D. W., Ch. 7 in "Organophosphorus Chemistry," Vol. 5, S. Trippett, Senior Reporter, The Chemical Society, London, 1973.

53. Ingold, C. K., "Structure and Mechanism in Organic Chemistry," 2nd ed., Cornell University Press, Ithaca, New York, N.Y., 1969, p. 1131.

54. Ishmaeva, E. A., Zimin, M. G., Galeeva, R. M., and Pudovik, A. N., *Izv. Akad. Nauk SSSR, Ser. Khim.*, [3], 538 (1971), *Chem. Abstr.*, **75**, 76925z (1971).

55. Islamov, R. G., Zimin, M. G., Dvoinishnikova, T. A., Pominov, I. S., and Pudovik, A. N., *Zh. Obshch. Khim.*, **47**, 1452 (1977); *Chem. Abstr.*, **87**, 151222w (1977).

56. Jugelt, W. Von., Andreae, S., and Schubert, G., *J. Prakt. Chem.*, **313**, 83 (1971).

57. Klinman, J. P. and Thornton, E. R., *J. Am. Chem. Soc.*, **90**, 4390 (1968).

58. Kluger, R. and Pike, D. C., *J. Am. Chem. Soc.*, **99**, 4504 (1977).

59. Konovalova, I. V., Burnaeva, L. A., Cherkena, M. V., and Pudovik, A. N., *Otkrytiya, Izobret., Prom. Obraztsy, Tovarnye Znaki*, **54**, 55 (1977); U.S.S.R. Patent 572,464 (Cl. CO7F9/02), 15 Sept, 1977; *Chem. Abstr.*, **88**, 7059b (1978).

60. Konovalova, I. V., Burnaeva, L. A., Yuldasheva, L. S., and Pudovik, A. N., *Zh. Obshch. Khim.*, 44, 2408 (1974); *Chem. Abstr.*, 82, 98071q (1975).

61. Konovalova, I. V., Burnaeva, L. A., Yuldasheva, L. S., and Pudovik, A. N., *Zh. Obshch. Khim.*, **46**, 1733 (1976); *Chem. Abstr.*, **85**, 177329v (1976).

62. Kost, D. and Sprecher, M. S., *Tetrahedron Lett.*, 4483 (1975).

63. Laskorin, B. N., Yakshin, V. V., and Sokal'skaya, L. I., *Zh. Obshch. Khim.*, **42**, 1261 (1972); *Chem. Abstr.*, **77**, 126780n (1972).

64. Lowry, T. H. and Richardson, K. S., "Mechanism and Theory in Organic Chemistry," Harper and Row, New York, 1976, p. 404.

65. McClellan, A. L., "Tables of Experimental Dipole Moments," Rahara Enterprises, El Cerrito, California, 1974, V. 2, p. 464.

66. McEwen, W. E. and Berlin, K. D., (Ed.), "Organophosphorus Stereochemistry," Dowden, Hutchinson and Ross, Inc., Stroudsburg, Pa., 1974, Part I and Part II.

67. Minkin, V. I., Osipov, O. A., Zhdanov, Y. A., "Dipole Moments in Organic Chemistry," W. E. Vaughan, (Trans. Ed.), Plenum Press, New York, N.Y., 1970, p. 240.

68. Olah, G. A. and McFarland, C. W., *J. Org. Chem.*, **36**, 1374 (1971).

69. Palaitis, W., Ph.D. Dissertation, University of Pennsylvania (1969); *Diss. Abstr.*, **31B**, 1210B (1970).

70. Pashinkin, A. P., Gazizov, T. Kh., and Pudovik, A. N., *Zh. Obshch. Khim.*, **40**, 28 (1970); *Chem. Abstr.*, **72**, 100827e (1970).

71. Pudovik, A. N., Batyeva, E. S., Nesterenko, V. D., and Anoshina, N. P., *Zh. Obshch. Khim.*, **44**, 1674 (1974); *Chem. Abstr.*, **82**, 4357n (1975).

72. Pudovik, A. N. and Gazizov, T. Kh., *Izv. Akad. Nauk SSSR, Ser. Khim.*, [9],1945 (1977); *Chem. Abstr.*, **87**, 200185x (1977).

73. Ramirez, F., Nowakowski, M., and Marecek, J. F., *J. Am. Chem. Soc.*, **99**, 4515 (1977).

74. Remizov, A. B., Gareev, R. D., and Pudovik, A. N., *Zh. Obshch. Khim.*, **42**, 1238 (1972); *Chem. Abstr.*, **77**, 100549u (1972).

75. Ramponi, G., Treves, C., and Guerritore, A., *Arch. Biochem. Biophys.*, **115**, 129 (1966).

76. Rao, C. N. R., "Water. A Comprehensive Treatise," F. Franks, (Ed.), Plenum Press, New York, 1972, V. 1, Ch. 3; and Goel, A., Murthy, A. S. N., and Rao, C. N. R., *Indian J. Chem.*, **9**, 56 (1971); and Hoyland, J. R. and Kier, L. B., *Theor. Chim. Acta.*, **15**, 1 (1969).

77. Rulison, D. S., Ph.D. Thesis, Oklahoma State University, May, 1968.

78. Samuel, D. and Silver, B. L., *J. Phys. Chem.*, **72**, 1809 (1968).

79. Savicheva, G. A., Gazizov, M. B., Razumov, A. I., *Zh. Obshch. Khim.*, **38**, 1093 (1968); *Chem. Abstr.*, **69**, 40706r (1968).

80. Schowen, R. L., *Prog. Phys. Org. Chem.*, **9**, 275 (1972).

81. Shagidullin, R. R., Chernova, A. V., *Probl. Org. Fiz. Khim.*, **132**, 41 (1971); *Chem. Abstr.*, **77**, 113272y (1972).

82. Shahak, I. and Peretz, J., *Israel. J. Chem.*, **9**, 35 (1971).

83. Skoog, D. A. and West, D. M., "Fundamentals of Analytical Chemistry," Holt, Rinehart and Winston, Inc., New York, 1963, p. 348.

84. Soroka, M. and Mastalesz, P., *Zh. Obshch. Khim.*, **44**, 463 (1974); *Chem. Abstr.*, **81**, 121058k (1974).

85. Stec, W. J., Van Wazer, J. R., Goddard, N., *J. Chem. Soc., Perkin Trans.*, **2**, 463 (1972).

86. Takamizawa, A., Harada, H., Patent Ger. Offen. 2,458,933 (Cl.C07 D), 26, Jun 1975, Japan; *Chem. Abstr.*, **83**, 114384x (1975).

87. Takamizawa, A., Hisao, S., *Yakugaku Zassi.*, **92**, 27 (1972); *Chem. Abstr.*, **76** 126899n (1972).

88. Takamizawa, A., Matsushita, Y., Harada, H., *Chem. Pharm. Bull.*, **25**, 991 (1977); *Chem. Abstr.*, **87**, 152064h (1977).

89. Takamizawa, A., Sato, H., *Chem. Pharm. Bull.*, **23**, 948 (1975); *Chem. Abstr.*, **83**, 178784K (1975).

90. Takamizawa, A., Sato, Y., and Tanaka, S., *Yakugaku Zasshi*, **85**, 298 (1965); *Chem. Abstr.*, **63**, 9941a (1965).

91. Taylor, H. A., M. S. Thesis, Oklahoma State University, May, 1964.

92. Terauchi, K. and Sakurai, H., *Bull. Chem. Soc. (Japan)*, **42**, 821 (1969).

93. Terauchi, K. and Sakurai, H., *Bull. Chem. Soc. (Japan)*, **43**, 883 (1970).

94. Trenbeath, K., Carraway, K. Durham, N. N., Narayanan, K. S., and Berlin, K. D., Unpublished results.

95. Van Wazer, J. R., Callis, C. F., Shoolery, J. N., and Jones, R. C., *J. Am. Chem. Soc.*, **78**, 5715 (1956).

96. Watanabe, M., *Bull. Chem. Soc. (Japan)*, **47**, 2048 (1974).

97. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968).

98. Wiberg, K. B., *Chem. Rev.*, **55**, 713 (1955).

99. Yamazaki, N. and Higashi, F., *Tetrahedron Lett.*, 5047 (1972).

100. Yeagle, P. L., Hutton, H. C., and Martin, R. B., *J. Am. Chem. Soc.*, **97**, 7175 (1975).

VITA 2

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Candidate for the Degree of

Doctor of Philosophy

Thesis: A STUDY OF KINETICS AND MECHANISM OF AQUEOUS AND ACID-CATALYZED HYDROLYSIS OF DIETHYL BENZOYLPHOSPHONATE BASED ON ^{31}P NMR, RAMAN, AND ULTRAVIOLET SPECTROSCOPIC ANALYSIS

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