# DIMETHYL N-ARYL PHOSPHORAMIDATES: STRUCTURAL EFFECTS ON BONDING AND SOLVOLYTIC REACTIVITY

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by

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ABSTRACT

The acid catalysed hydrolysis of a number of ring alkyl substituted dimethyl N-aryl phosphoramidates, $(MeO)_2P(O)NHAr$, has been studied by measuring the rates of hydrolysis with the aid of a UV spectrophotometer. These rates have been correlated with the pKa values of the corresponding anilinium ions and the slope of this reactivity-basicity relationship for phosphoramidate with ortho substituents ($\beta$ = 0,85) is found to differ from that for substrates with meta and para substituents ($\beta$ = 0,36). Determination of the thermodynamic parameters indicates that the entropy of activation is approximately constant for the substrates studied and the strongly negative values ($\Delta S^{\neq}$ = 155,4 ± 17,5 J $mole^{-1}K^{-1}$) are consistent with an A2 type mechanism. The constancy of kinetic solvent isotope effect values ($k_{H_2O}/k_{D_2O}$ = 0,52 ± 0,04) confirms that the hydrolysis reaction for these phosphoramidates proceeds via the same mechanism for all substrates. We propose that the difference in slopes of the reactivity-basicity relationship between ortho substituted phosphoramidates and meta and para substrates is primarily due to solvation having different effects on the protonated substrate. We therefore conclude that the A2 type mechanism is a crude model since it ignores these effects completely.

The infrared stretching frequency of the phosphoryl group has been measured for a series of ring substituted N-aryl phosphoramidates where the ring substituents vary between strong electron donating to strong electron withdrawing groups. The substituent induced shifts have been compared with analogous effects in acetanilides. It has

been found that intermolecular hydrogen bonding strongly affects the $\nu_{po}$ values in phosphoramidates and, with the exception of the sterically hindered structures, these effects are still present in dilute solutions.

Hammett's correlations of the $\Delta\nu_{po}$ and $\Delta\nu_{co}$ shifts indicate that the transmission of the resonance effects of substituents to the phosphoramidate group is negligible in comparison with the carboxyamide function.

CONTENTS

# CHAPTER ONE

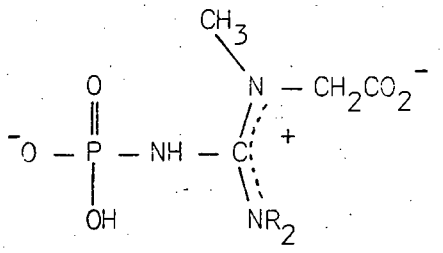
# INTRODUCTION

# I. INTRODUCTION

## I.1 The role of phosphoryl compounds

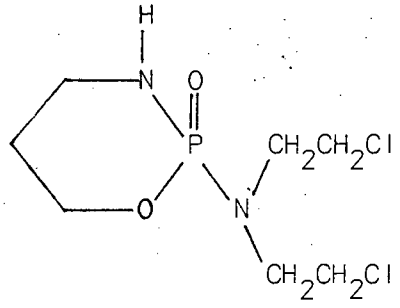
There has been considerable interest in the chemistry of compounds with phosphorus-nitrogen bonds[1] since the lability of the P-N bond plays an important role in biochemical systems for phosphorylation of various substrates. One of the most well known examples is the function of phosphorocreatine (PC) as a phosphagen, phosphorylating ADP to generate ATP in a reaction catalysed by creatine kinase. (Equation I).

$$H^+ + ADP + PC \underset{Mg^{+2}}{\rightleftharpoons} ATP + creatine \qquad \text{(Eq. I)}$$



(PC)

Phosphoramide mustards ( $P(O)N(CH_2CH_2Cl)_2$ ) are being studied for use in cancer chemotherapy.[2] It is envisaged that these compounds can act as potential alkylating agents which might be selectively "activated" in tumors by enzymatic release of nornitrogen mustard, $[HN(CH_2CH_2Cl)_2]$. cyclophosphamide (I) has been found to exhibit anti cancer activity towards a relatively wide spectrum of human cancers.



(I)

Interest in compounds containing a P-N bond has also increased since the

discovery that some of these compounds exhibit remarkable toxic properties towards mammals and insects.[3] In particular, phosphoramidates, which are esters of phosphoramidic acid $(HO)_2P(O)NH_2$ are considered important as pesticides[4] and several of them including schradan (octamethylpyrophosphoramide), ruelene (4*t*-butyl-2-chlorophenyl methyl N-methyl phosphoramidate) and zytron (2,4 dichlorophenyl methyl N-isopropylphosphoramidothiolate) are commercially available.

It has been necessary to obtain more precise information on the physicochemical properties of this type of compound since even though there is a relatively large amount of work recorded on the cleavage of the P-N bond under acidic catalysis conditions in such compounds as phosphoramidic acid and N-substituted phosphoramidic acids, there are relatively few publications dealing with the kinetics of acid hydrolysis of phosphoramidates.

In acid catalysed solvolysis studies of compounds containing a P-N bond, the general mechanism can be considered to be as follows:[4,5]

$$A + H^+ \underset{}{\overset{\text{fast}}{\rightleftharpoons}} AH^+ \xrightarrow{\text{slow}} A^{\neq} \longrightarrow \text{products} \qquad \text{(Eq. II)}$$

where $A = X(Y)P(O)NR_2$

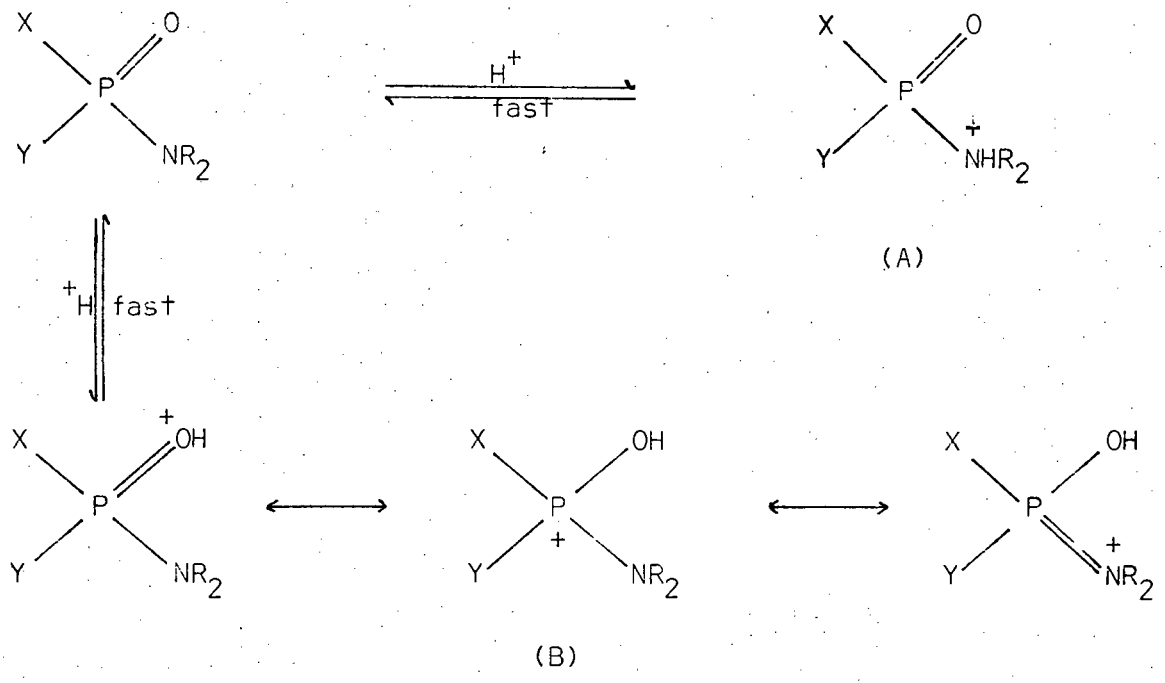
Rapid protonation of the substrate A preceeds the rate determining cleavage step.

From equation II it can be seen that two considerations must be taken into account, *viz.* (A) site of protonation and (B) whether the reaction proceeds *via* a unimolecular (dissociative) or bimolecular (associative) mechanism.

A. Site of protonation

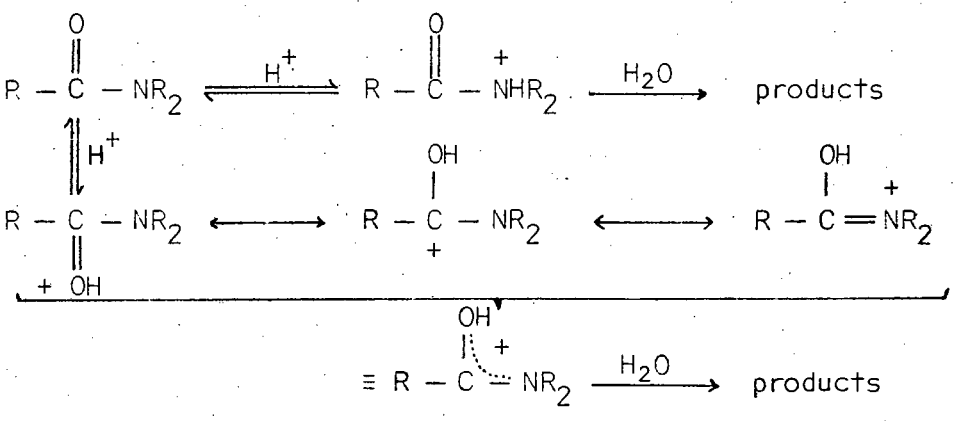
The substrate $X(Y)P(O)NR_2$ has both oxygen and nitrogen atoms as basic centres

and under acidic conditions, the fundamental mechanistic problem involves the structure of the substrate conjugate acid, *i.e.* the phosphoramidonium ion.



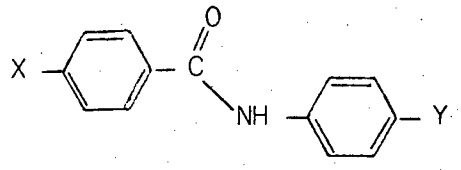

(Eq. III)

This system is therefore analogous to the acid catalysed hydrolysis of carboxylic amides where the general reaction is given by equation IV.




(Eq. IV)

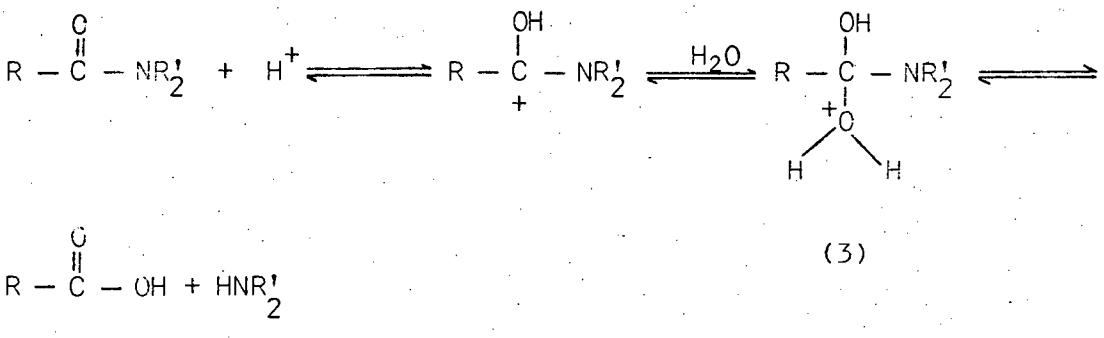
In their study of substituted benzanilides (2), Locerente *et al*[6] found that rates of hydrolysis were higher when Y was an $\bar{e}$ accepting group and thus concluded that this does not allow a mechanism including an intermediate N protonated amidonium ion.



(X,Y = H, OMe, Me, Cl, $NO_2$)

(2)

It is generally agreed that O rather than N protonation is predominant in carboxylic amides[7-10] and that the reaction proceeds *via* a tetrahedral intermediate (3) in equation v.

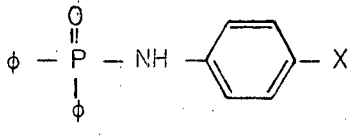


(Eq. V)

(3)

The principal difficulty in establishing the protonation behaviour of phosphoric amides is due to its high instability in acidic solutions, so that direct investigation of the protonated species is in most cases not possible. The following arguments however seem to strongly indicate that N protonation is favoured in this class of compounds.

In working with structure-reactivity corellations of phosphinanilides (4), Haake *et al*[1] proposed that acid catalysed hydrolysis of these compounds proceeded *via* the N protonated species.

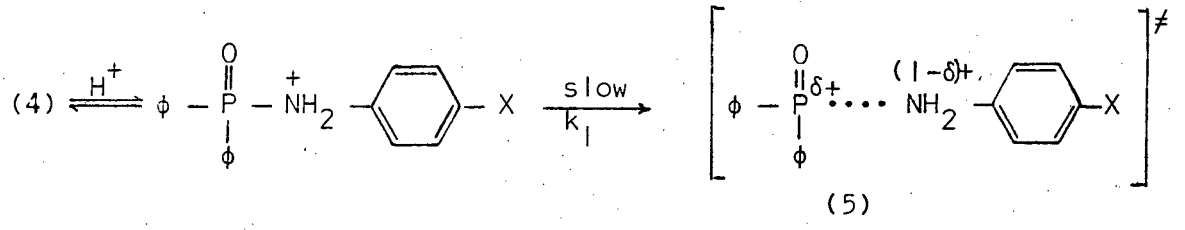


(X = $NO_2$, Cl, $CH_3O$)

(4)

Their values for the Hammett reaction constant ($\rho$ = -1,73) and ($\rho^*$ = -1,0)[11] are of opposite sign to that obtained by Lockerente[6] for benzanilides

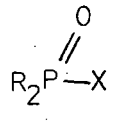
($\rho$ = +1,66). If hydrolysis of (4) were proceeding *via* protonation on oxygen followed by bimolecular reaction with water, $\rho$ would be expected to be positive as for the benzanilide system. Haake thus proposed the mechanism (equation VI) in which the transition state (5) has a positive charge on the nitrogen, thereby leading to a negative value for $\rho$.



(Eq. VI)

(5)

A plot of log $k_1$ for phosphinanilides[1] (4) and phosphinamides[11] (6) against pKa values for the corresponding anilinium ions gave linear free energy relationships with positive values for the slopes. This suggests that the transition states have considerable anilinium ion character and are therefore consistent with reaction through an N protonated species.



(6)

(a) R = $-C_6H_5$ X = $-NH_2$

(b) R = $-C_6H_5$ X = $-NHCH_3$

(c) R = $-C_6H_5$ X = $-N(CH_3)_2$

(d) $R_2$ = $-C(CH_3)_2CH(CH_3)C(CH_3)_2-$ X = $-N(CH_3)_2$

(e) R = $-CH(CH_3)_2$ X = $-N(CH_3)_2$

Haake[11] found that the phosphinamide (6a) undergoes acid catalysed hydrolysis $10^5$ times more rapidly than the corresponding carboxylic amide $C_6H_5$-C(O)$NH_2$. In our study of phosphoramidates, it was found that the N-p-methylphenyl-dimethylphosphoramidate $(MeO)_2P(O)$-$NHC_6H_4Me$(P) was hydrolysed in acid medium, $10^2$ times faster than the corresponding benzanilide.[6] This lability of the P-N bond in phosphoric amides compared with the C-N bond in carboxylic amides in acid media can be considered to be due to the greater basicity and better leaving ability of the protonated amino substituent.

Garrison and Boozer[4] proposed that O protonation of phosphoramidates $(RO)_2P(O)\text{-}NR'_2$ is possibly more important than in carboxylic amides but do not give any direct evidence to support this. They state that the phosphoryl group is more polar than the carbonyl group and as such there should be a marked tendency for the formation of a $p\pi\text{-}d\pi$ bond between the nitrogen and phosphorus atoms. The nitrogen atom would tend to be less basic because of this donor-$\pi$ bond formation. However $^{13}C$ NMR experiments on N phosphorylated aniline and O phosphorylated phenols (7) using the dual substituent parameter approach,[12] were found to indicate no significant $p\pi\text{-}d\pi$ back donation from Y to the phosphorus atom in these systems.

$\phi - Y - \overset{O}{\overset{\|}{P}}(OEt)_2$ (Y = NH, O)

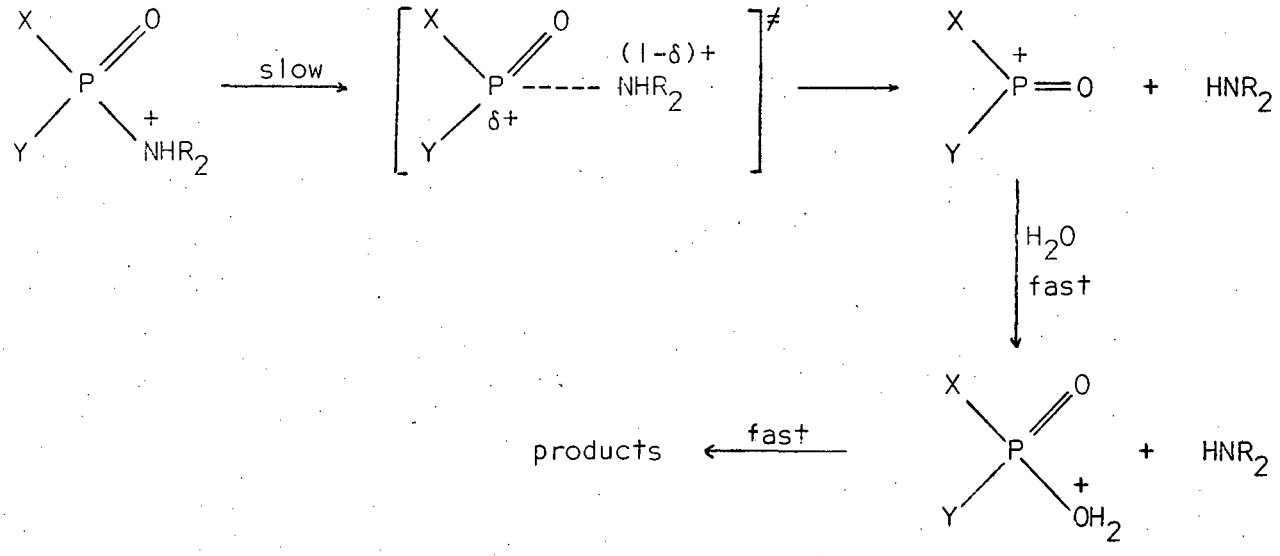
(7)

This was also evident from molecular orbital calculations performed on O and N protonated phosphoric amides.[13] The concept of N protonation has also been supported by studies of the effects of protonation upon the PNCH and POCH coupling constants in some phosphinic amides and esters.[14] O protonation cannot be discounted completely and possibly exists in equilibrium with the N protonated species (Equation III) but it seems reasonable to believe that it is the N protonated species which is the kinetically reactive species in a solvolysis reaction.

B. A1 *vs* A2 reaction

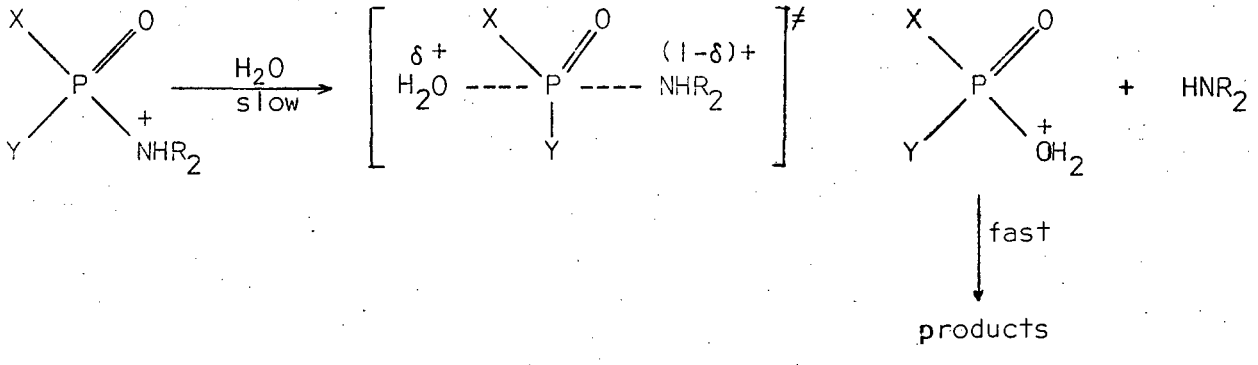
The acid catalysed hydrolysis of phosphoric amides must now be considered in terms of the mechanism of the P-N bond cleavage.

In the A-1 type mechanism, unimolecular P-N bond cleavage is followed by rapid reaction with water (Equation VII).




(Equation VII)

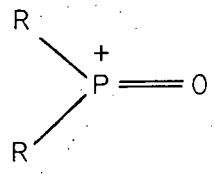
In the A-2 type mechanism, direct substitution of water involving a rate determining one step process occurs in which the P-N bond is broken at the same time that the water molecule attacks the phosphorus atom. (Equation VIII).




(Equation VIII)

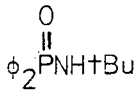
Although the contribution of an A-1 pathway has been suggested for some phosphoric amides, the generality of the bimolecular $S_N2(P)$ mechanism seems well established. Haake[1] and his co-workers suggested that phosphinamides undergo acid catalysed hydrolysis *via* both A1 and A2 mechanisms, depending on the nucleophilicity of the leaving group. Work done by

Harger[15] on phosphinamides and Haake[16] on phosphinyl chlorides indicate that these compounds are generally reluctant to react by a dissociative SN1(P) mechanism,[17] presumably due to the instability of the phosphinylium cations (8).



(8)

Most of the work done on phosphoric amides indicates that the SN2(P) mechanism is favoured. Modro and co-workers[18] in their study of phosphinates (9) and phosphoramidates (10) found that for P-N bond cleavage, the rate-acidity dependence showed behaviour typical for the A2 mechanism.



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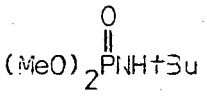
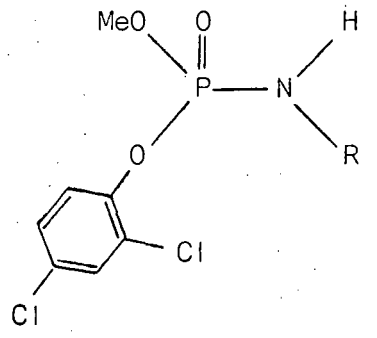


(10)

Values for the kinetic solvent isotope effect for substitution at phosphorus were also typical for the A-2 type mechanism.

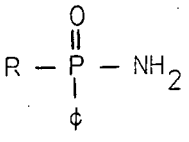
In their work on 2,4-dichlorphenyl methyl N-alkyl phosphoramidates (11), Garrison and Boozer[4] obtained strongly negative entropies of activation ($\Delta S^{\neq}$ = -30 to -35 eu) which are indicative of a reduction in the number of degrees of freedom in the transition state and occur when the water molecule attacks the phosphoryl group. (Unimolecular acid catalysed reactions have small activation entropies of either sign.[19,20]). Garrison and Boozer[4] also noted that an increase in the bulk of the substituent R on the nitrogen atom in (11) caused a reduction in the reaction rate. This is consistent with a bimolecular reaction where addition of water to the phosphoryl group



R = alkyl

(11)

results in an increase of coordination number of phosphorus from 4 to 5 in going from the ground state to the transition state (Equation VIII). Similarly, Harger[21] found that values of rate constants for acid catalysed hydrolysis of (12) and (13) decreased with increasing bulk of substituent R on phosphorus.



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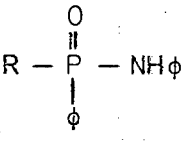
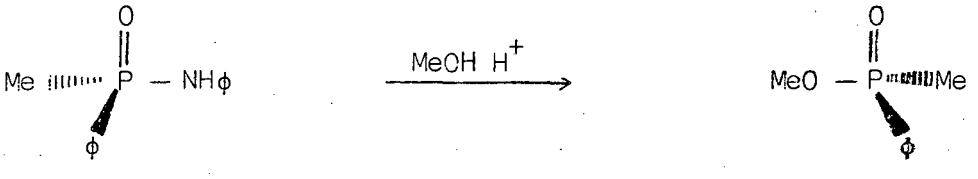


(13)

R = Et, cyclopropyl, $Pr^{i}$, 1-methylcyclopropyl, $Bu^{t}$.

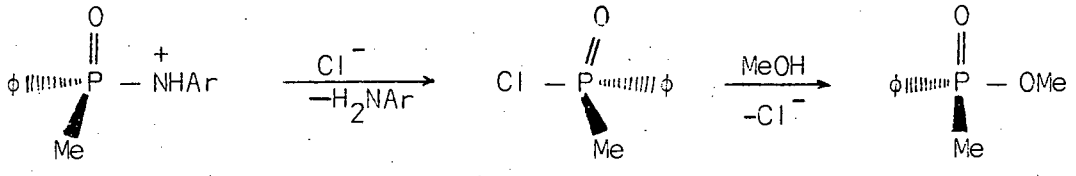
This also encourages the view that these compounds react by an associative (A2) mechanism.

In his studies of the methanolysis of optically reactive methyl phenyl phosphinanilide, Haake[1] reports predominant inversion of configuration which infers on A2 type mechanism.



Koizumi[22] is of the opinion that the mechanism is dependent on the acidity of the medium and that the Al reaction path increases in importance with increasing acidity of the medium.

Harger[15] however disagrees with this "merged Al-A2" mechanism and found that his work on the solvolysis of alkylphenylphosphinic amides seemed incompatable with such a theory. One of the mechanisms which he proposed involves the double inversion due to nucleophilic catalysis by a chloride ion (Equation IX).



(Equation IX)

Since the acid is also a source of the nucleophile, the catalytic pathway, with retention of configuration, would be sensitive to the concentration of the hydrogen chloride. At low concentrations of HCl it might account for a negligibly small proportion of the section, so that methanolysis would in effect proceed entirely by the uncatalysed pathway with inversion of configuration, while at high concentration of HCl it could become the major pathway and cause the majority of the product to be formed with overall retention of configuration.

Further evidence for the preferential A2 type reaction path has been obtained from work done on phosphacyl chlorides and includes (a) rate enhancement on addition of nucleophilic reagents,[23] (b) rate dependence on the size of the nucleophile,[24] (c) steric retardation by large substituents at phosphorus;[25] and (d) rate inhibition due to angle strain at phosphorus.[26] In general therefore,

most of the evidence seems to indicate the predominance of an associative A-2 type mechanism for molecules containing a phosphoryl group.

## I.2 The determination of a L.F.E.R. using IR spectrophotometry.

In another aspect of the project it was decided to investigate substituent effects upon the vibrational frequencies of the phosphoryl group in the ring substituted N-phenylphosphoramidates (I4) and relate them to analogous effects in the carboxylic derivatives (I5).

$X - C_6H_4 - NHP(O)(OR)_2$ (I4)

$X - C_6H_4 - NH - C(O)R$ (I5)

The substituent constants in general use are the sigma values first introduced by Hammett[27] and the effect of a substituent on some physical property of a reaction for example, equilibrium or reaction rate, was correlated by the Hammett equation (Equation X).

$$\text{Log}\frac{K}{K_o} = \rho\sigma \qquad \text{(Eq. X)}$$

$\rho$ is the reaction constant and varies according to the electronic demand of the reaction or property measured but is a constant for a fixed set of conditions. The substituent constant $\sigma$ gives a measure of a substituents electronic effect on the reaction or measurement centre, providing steric effects are absent. Taft[28] proposed that these substituent constants were composed of both inductive and resonance contributions. The inductive part is considered to be due to the electrical perturbation transmitted both through the $\sigma$ bonds and through space, arising from the charge distribution in the substituent. The resonance part is considered to be due to the perturbations observed in the $\pi$ system of the ring. Hence we can write:

$$\sigma = \sigma_R + \sigma_I \qquad \text{(Eq. XI)}$$

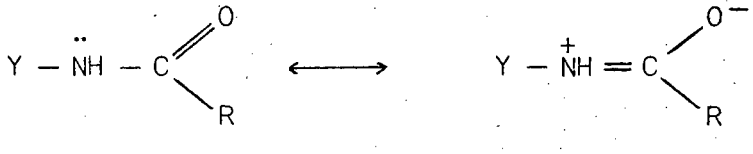
Since the σ constant as defined in equation X are in energy units, a relation of the form

$$\nu - \nu_0 = \rho\sigma \qquad \text{(Eq. XII)}$$

may be employed to correlate infrared frequency data. (Since $\nu^2$ is related to the force constant of a bond, it was at one stage felt[29] that this value, rather than the value for ν should be correlated with σ. However σ values are expressed in energy units and so might reasonably be related to ν.)

This infrared approach has been successfully applied to carbonyl compounds where the $\nu_{CO}$ values correlate with the structural variations according to the Linear Free Energy relationship given by equation XII. For example, $\nu_{CO}$ values for the para-substituted acetophenones correlate well with substituent constants, and the dual substituent parameters (dsp) analysis shows similar contributions of resonance and inductive effects.[30,31]

In carboxylic amides (16) variation in the N substituent Y should affect the resonance and thus modify the $\nu_{CO}$ value:



(16)

However Richards and Thompson[32] pointed out that significant spectral changes observed for carboxylic amides are caused by hydrogen bonding effects. This was further supported by Klemperer *et al*[33] in their work on secondary amides. They found that in all cases studied, the carbonyl stretching frequency moved to a higher frequency upon dilution and proposed

that the lower frequencies were due to hydrogen bonding to the carbonyl oxygen. Reliable results on the structural effects can therefore be obtained only in dilute solutions in non polar solvents.

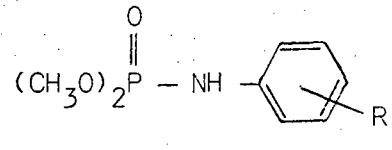
In acetanilides (15; R = Me) the detailed electron distribution in the amide group should be sensitive to the ring substitution, changing the availability of the nitrogen lone pair for conjugation with the carbonyl group. For a series of ring substituted acetanilides it was found that the value of $\nu_{CO}$ (str) depends on the substituent, and for the typical meta and para groups, a variation within the range of 24 $cm^{-1}$ was observed.[34] We have correlated the reported values of $\nu_{CO}$ vs $\sigma_X$ constants and obtained a fair linear relationship (r = 0,980) with, as expected, positive slope of the $\Delta\nu_{CO}$ vs $\sigma_X$ plot. Direct comparison of substituent effects on the stretching frequency of the carbonyl group in (15) with the corresponding effects upon the phosphoryl group in N-arylphosphoramidates (14) should provide insight into the bonding characteristics of these two amide systems.

Relevant studies in the area of the phosphoric amides are scarce. The variation in the $\nu_{PO}$ and $\nu_{PN}$ frequencies for the diethylphosphoramidates $(EtO)_2P(O)NR_2$ (R = H, Me, Cl) was discussed in terms of the $p_\pi - d_\pi$ bonding.[35] Infrared spectra of phosphinamidates,[36] phosphoramidates,[37] and phosphazenes[38] revealed significant intermolecular hydrogen bonding, lowering the $\nu_{PO}$ value to ca. 1220 $cm^{-1}$ (for the amides free of hydrogen bonding $\nu_{PO}$ = 1270-1280 $cm^{-1}$). Although in his classical review of the infrared spectra of organic molecules, Bellamy[39] formulates the opinion that for phosphoramidates "P=O frequencies revert to normal in dilute solution", in work on organophosphorus esters, acids and amines[36] he showed that hydrogen bonding in solutions of these derivatives causes a considerable decrease in frequency of the P=O absorption. Analysis of

the NH stretching and bending absorption bands for N-alkylphosphoramidates led Nyquist[40] to the conclusion that at concentrations of $10^{-2}$ M or less, the intermolecular hydrogen bonding effects are absent. For a proper treatment of the substituent effects it is therefore essential to bear in mind the fact that substituents can modify bonding of the phosphoryl group *via* the intramolecular electronic effects as well as due to the change in the hydrogen bonding interactions.

## 1.3 Objectives

In view of the work reported in the literature, it was decided to perform a study on a series of ring substituted phosphramidates (17).



(17)

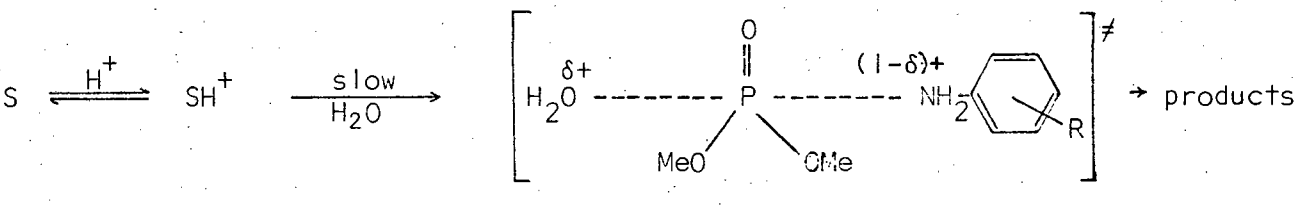
(a) R = H; 2-Me; 3-Me; 4-Me; 3,4 di Me; 2,6 di Me; 2 Et; 4 Et; 4 *n* Bu; 2 *t*Bu; 4 *t*Bu. The N-methyl derivative was also prepared for comparative purposes.

(b) R = 4-Ph; 3-F; 4-F; 3-OMe; 4-OMe; 3-$NO_2$; 4-$NO_2$; 4-$NMe_2$.

A closely related group of alkyl substituted phosphoramidates (17a) with alkyl groups in all possible positions, were prepared for studies of the kinetics of the acid catalysed hydrolysis of these compounds. Alkyl groups were chosen as substituents as they have similar electronic effects and the sensitivity of the P-N bond to acid catalysed hydrolysis with variations of inductive and resonance effects of substituents could be accurately determined. Protonation and solvation effects could also be expected to be similar for these compounds since there could be no interferance due to protonation of substituent as would be the case for substituents with non-bonding electrons such as most of those in group (17b).

The following studies were to be performed on the phosphoramidates (17a) as they could provide essential information on the mechanism of acid catalysed hydrolysis of these compounds.

(i) A linear free energy relationship was to be derived in the form of a reactivity-basicity plot. $PK_a$ values give a good indication of inductive and resonance effects but due to the lability of phosphoramidates in acidic media, it is difficult to determine these values. However, in the transition state, (18), the leaving anilinium group resembles a protonated aniline and thus $pK_a$ values for the corresponding anilines could be used.




(18)

(Equation XIII)

It is important to note that any group R which increases the basicity of the aniline group in the phosphoramidate will favour the pre-equilibrium protonation step but will disfavour the slow step (equation XIII). The observed rate is thus a result of these two opposing effects. A linear correlation with a positive slope indicating that acidic hydrolysis proceeds *via* the N-protonated species, was expected. (For carboxylic amides a negative slope is obtained).

(ii) In order to ascertain whether the acid catalysed hydrolysis of the phosphoramidates (17a) proceeded *via* an A1 or A2 type mechanism, the Arrhenius parameters, *i.e.* activation energy, $E_a$; free energy of activation, $\Delta G^{\neq}$; entropy of activation, $\Delta S^{\neq}$ and enthalpy of activation, $\Delta H^{\neq}$; for the transition state complex, were to be determined by observing rates of

hydrolysis of these compounds at varying temperatures. Strongly negative values for $\Delta S^{\neq}$ would indicate an A2 type mechanism while positive values or values close to zero would indicate an A1 type mechanism.[41]

(iii) Kinetic Solvent Isotope Effects generally supply information on the protonation step in the mechanism and thus they were determined for a representative cross section of the phosphoramidates (17a). $D_2SO_4$ is a stronger acid than $H_2SO_4$ and thus for the protonation in the pre-equilibrium step, the concentration of the deuterated substrate ($SD^+$) in equation XIII will be higher and the overall rate will therefore be increased. For an acid catalysed reaction with a reversible proton transfer prior to the rate determining step,[42]

$$k_{H_2O}/k_{D_2O} < 1$$

For a mechanism involving a proton transfer in the transition state

$$k_{H_2O}/k_{D_2O} > 1$$

The variation in the infrared spectroscopic properties of phosphoramidates (17a and b) was also studied in order to ascertain any correlation with the variation of substituents. The effect of the substituents on the P=O stretching frequency was studied using infrared, since it is the most polar group and it contains a multiple bond. Changes in bond order with change in substituent could therefore easily be monitored. This could be correlated with similar work performed on carboxylic amides.

# CHAPTER TWO

# DISCUSSION AND RESULTS

# 2 RESULTS AND DISCUSSION

## 2.1 Acid catalysed hydrolysis

The reaction studied can be represented by the general equation:

$$(MeO)_2P(O)\text{-}NHAr + H_2O + H^+ \longrightarrow (MeO)_2PO_2H + Ar\text{-}NH_3^+ \qquad \text{(Eq. XIV)}$$

It is a well-established fact that under acidic conditions, phosphoric amide bond (P(O)-N) is much less stable than the corresponding ester function (P(O)-O).[43] It was therefore assumed that the only reaction occuring is the formulation of the anilinium ion according to the equation XIV. However, since the analytical method used (UV spectrophotometry) detects only the P-N bond cleavage (release of the anilinium ion), our results would not be affected even if the dimethyl phosphoric acid initially formed underwent further hydrolysis.

### 2.1.1 Kinetic determination

The rate of a reaction is usually expressed as the rate of change of concentration with time, at a constant temperature and volume.[44] For a first order reaction the rate of the reaction depends only on the first power of the concentration of a single reacting species and the rate law can be written as

$$-\frac{dc}{dt} = kc \qquad \text{(Eq. XV)}$$

where k is the rate constant and has the units of the reciprocal of time. If the initial concentration, at time t = 0, is Co and if at some later time, t, the concentration has fallen to C, we can integrate equation XIV to get

$$-\int_{Co}^{C} \frac{dc}{C} = k\int_{o}^{t} dt$$

$$\therefore \quad -\ln \frac{C}{Co} = kt$$

or $$\ln C = -kt + \ln Co \qquad \text{(Eq. XVI)}$$

From the Beer-Lambert law[45]

$$\log \frac{Io}{I} = \varepsilon C \ell$$

where Io = initial intensity of monochromatic light

I = intensity of the monochromatic light after passing through a sample

$\varepsilon$ = molar extinction coefficient

C = concentration (in moles per liter)

$\ell$ = path length of curvette (in cm).

The absorbance $A = \log \frac{Io}{I}$

$$\therefore \quad A = \varepsilon C \ell$$

$$\therefore \quad C = \frac{A}{\varepsilon \ell}$$

For a 1 cm path length curvette which was used in our experiments

$$C = \frac{A}{\varepsilon}$$

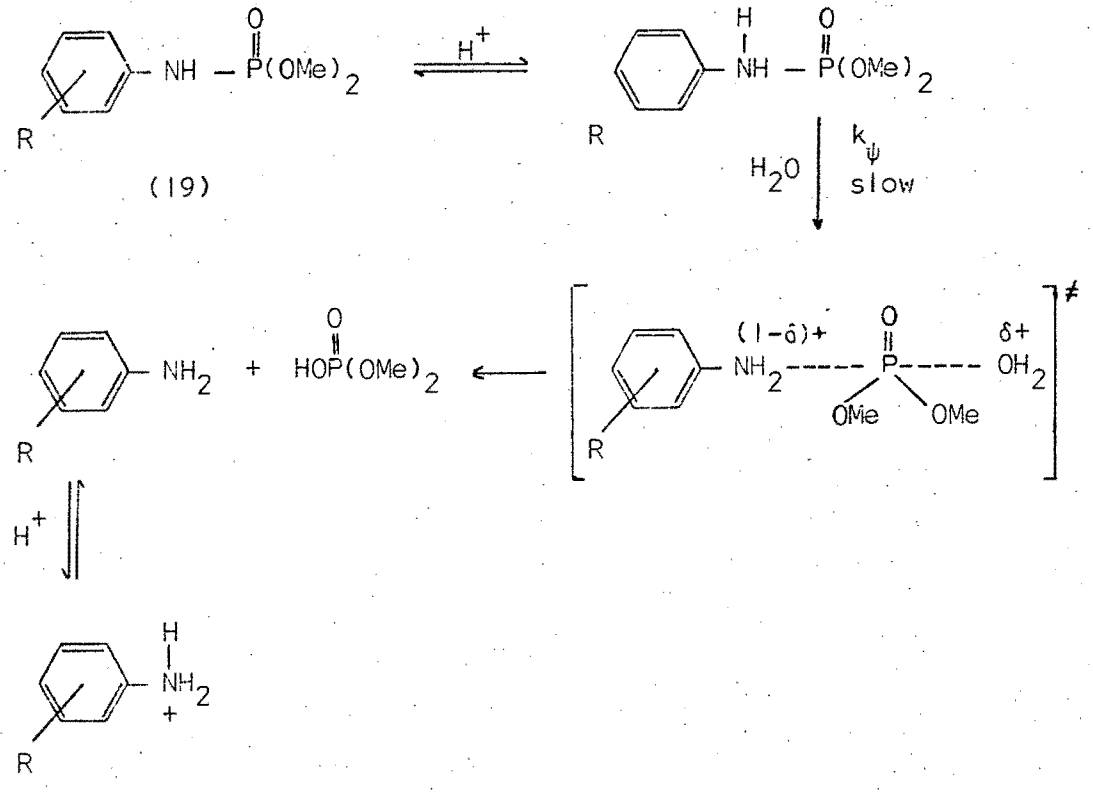
Substituting into equation XV

$$-\ln \frac{A}{Ao} = kt$$

and $$\ln A = -kt + \ln Ao \qquad \text{(Eq. XVII)}$$

where Ao is the initial absorbance of a solution with initial concentration Co.

The rates of acid catalysed hydrolysis of the phosphoramidates (17a) can be accurately monitored using UV spectrophotometric techniques. The phosphoramidates are all amides and as such are relatively weak bases and can be expected to exist mainly as the neutral molecule (19) in acidic solution. The absorbance due to $n \rightarrow \pi^*$ transitions is relatively strong compared with the corresponding aniline which is a much stronger base than the phosphoramidate and exists almost entirely as the protonated species (20) in acidic solution.



(Eq. XVIII)

(19) (20)

A large change in absorbance is thus observed in this hydrolysis reaction with the absorbance of the products dropping almost to zero (Figure 2.1).

From equation XVIII it is obvious that the rate of the reaction is dependent upon the concentration of both the phosphoramidate and the

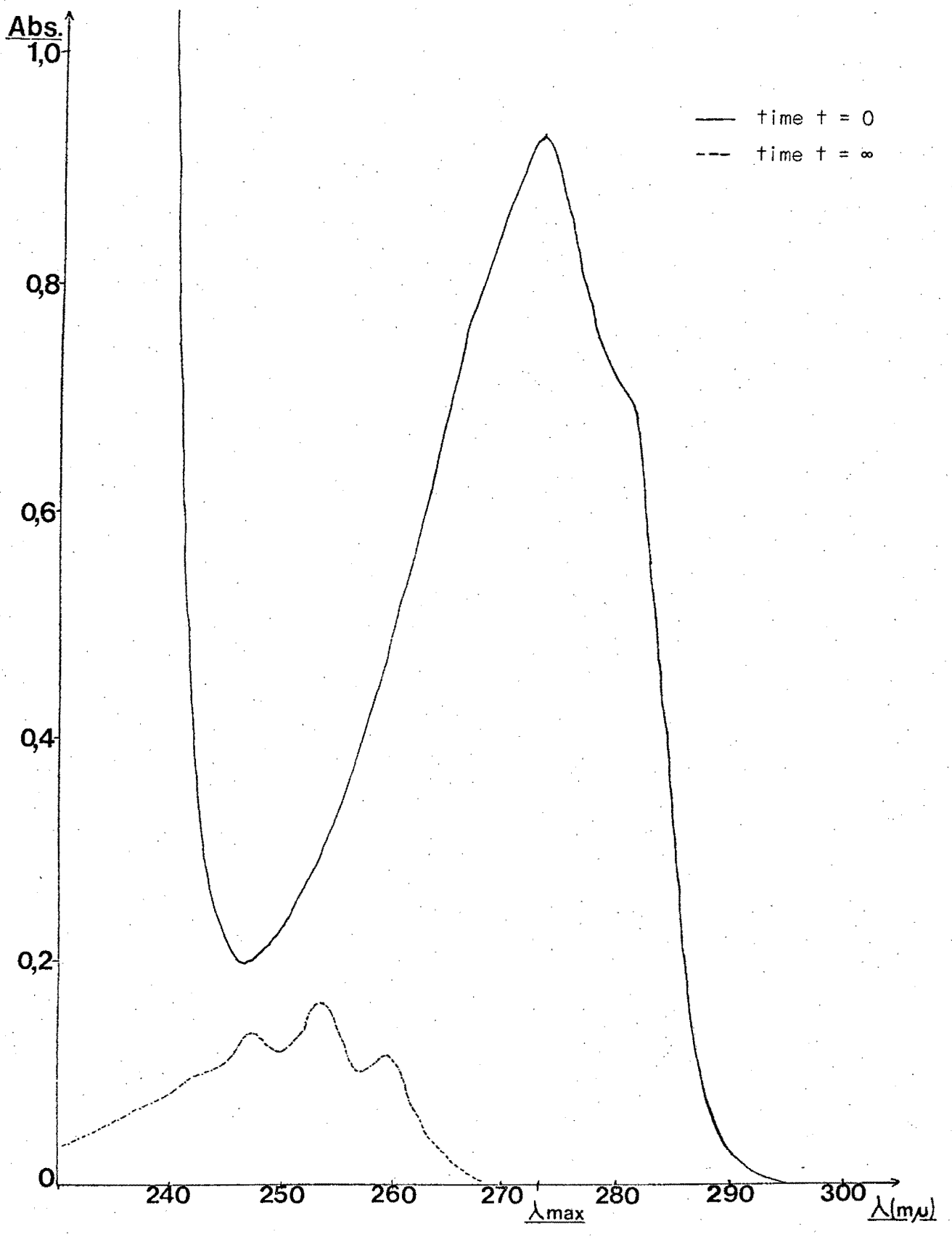



**Fig. 2.1**

Absorbance vs. wavelength for
dimethyl N-phenyl phosphoramidate

nucleophile which in this case is water. It is thus a second order reaction but since the water is present in great excess and its concentration remains effectively constant throughout the reaction, the reaction may be considered to be pseudo-first order.

Beer's law was found to be satisfied over the concentration range of the phosphoramidates studied, the details of which are described in chapter 3 section 3.4.

A plot of ln(Absorbance) of phosphoramidate against time gave always a linear plot (for example Figures 4A-4D) which indicates that the acid catalysed hydrolysis of phosphoramidates does indeed proceed *via* a pseudo first order reaction. A linear regression was performed on these values (for example Tables 4.1 - 4.4) to obtain a "best fit" curve and the observed rate constant, $k_\psi$, was calculated from the slope of this plot. The molecular extinction coefficient, $\varepsilon$, was calculated from the intercept on the Y axis ($\ln A_o$) since the absorbance at time $t = 0$ could not be measured due to the rapid hydrolysis of the phosphoramidates in the acidic media.

The half life of the hydrolysis reaction was calculated from the equation

$$t_{\frac{1}{2}} = \frac{0{,}6931}{k_\psi}$$

where $k_\psi$ is the observed rate constant.

Values for the basicity constants (pKa) were given only for anilines in water at 25°C[46] but we found that our substrates were insoluble under these conditions. Dioxane was therefore used as a co-solvent and it was found that a solution of 20% dioxane in water was a suitable

solvent for the phosphoramidates (17a). It was assumed that the effect of the dioxane on the pKa values would be the same* for all the anilines and since the difference in these values was used in the reactivity-basicity relationship (Figure 2.2) the slopes of this relationship would remain unaffected.

The validity of our results is supported by the excellent reproducibility of the rate constants as well as the high correlation coefficients obtained from the linear regression calculations. (Reactions were monitored for 2,7 - 5,7 half lives but on average, a period of 3,5 half lives (over 85% of conversion) was found to be suitable). The wavelengths at which the absorbance measurements were made varied between 270 mμ and 280 mμ and are indicated in tables 4.5 - 4.7.

No specific studies were performed to determine the effect of variation of initial concentration, Co, of the substrate on the rate constant but from table 4.5 it can be seen that for variations of up to 2,4 fold in Co, there is no effect on the rate constant.

The mean rate constants from tables 4.5 and 4.6 are listed in tables 2.1 and 2.2 respectively. Since tables 4.5 and 4.6 list data for rate determinations performed in media with slightly different acid concentrations, only the mean value of the relative rates** for these two sets

---

* Since all the pKa values (with an exception of that for N-methylaniline) used for correlation refer to the primary anilinium ions ($Ar\text{-}NH^{+}$), any hydrogen bonding due to the presence of dioxane should be the same for all members of a series.

** The relative rate is expressed as

$$k_{rel} = \frac{\text{rate constant for dimethyl N-(alkyl substituted phenyl) phosphoramidates}}{\text{rate constant for dimethyl N-(phenyl) phosphoramidate}}$$

$$= k_R/k_H$$

TABLE 2.1 [a]

| R | Mean $k_\psi$ ($\times 10^{-4} sec^{-1}$) | Std. Dev. ($\times 10^{-4} sec^{-1}$) | $k_{rel}$ | log $k_{rel}$ | pKa[b] | ΔpKa |
|---|---|---|---|---|---|---|
| H | 1,1498 | 0,0435 | 1 | 0 | 4,60 | 0 |
| 2 Me | 0,8060 | 0,0130 | 0,7009 | -0,1543 | 4,45 | -0,15 |
| 3 Me | 1,1652 | 0,0440 | 1,0134 | 0,0058 | 4,71 | 0,11 |
| 4 Me | 1,8409 | 0,0152 | 1,6010 | 0,2044 | 5,08 | 0,48 |
| 3,4 diMe | 1,5740 | 0,0272 | 1,3689 | 0,1364 | 5,17 | 0,57 |
| 4 Et | 1,6174 | 0,0006 | 1,4066 | 0,1482 | 5,00 | 0,40 |
| 2 Et | 0,5082 | 0,0043 | 0,4419 | -0,3547 | 4,30 | -0,30 |
| 4*n* Bu | 1,5209 | 0,0221 | 1,3227 | 0,1215 | - | - |
| 4*t* Bu | 1,2458 | - | 1,0835 | 0,0348 | 4,95 | 0,35 |

[a] See chapter 4 for meaning of symbols. [b] Values from reference 46.

TABLE 2.2

| R* | Mean $k_\psi$ ($\times 10^{-4} sec^{-1}$) | Std. Dev. ($\times 10^{-4} sec^{-1}$) | $k_{rel}$ | log $k_{rel}$ | pKa | ΔpKa |
|---|---|---|---|---|---|---|
| H | 1,2317 | 0,0060 | 1 | 0 | 4,60 | 0 |
| 2 Me | 0,8393 | 0,0259 | 0,6814 | -0,1666 | 4,45 | -0,15 |
| 3 Me | 1,2478 | 0,0356 | 1,0131 | 0,0056 | 4,71 | 0,11 |
| 4 Me | 1,9436 | 0,0071 | 1,5780 | 0,1981 | 5,08 | 0,48 |
| 3,4 diMe | 1,9006 | 0,0625 | 1,5431 | 0,1884 | 5,17 | 0,57 |
| 2,6 diMe | 0,3413 | 0,0418 | 0,2771 | -0,5574 | 3,95 | -0,65 |
| 2 Et | 0,5332 | 0,0139 | 0,4329 | -0,3636 | 4,30 | -0,30 |
| 4 Et | 1,7290 | 0,0395 | 1,4038 | 0,1473 | 5,00 | 0,40 |
| 2*t* Bu | 1,3072 | 0,0046 | 1,0613 | 0,0258 | 5,03 | 0,43 |
| 4*t* Bu | 1,3623 | 0,0204 | 1,1060 | 0,0438 | 4,95 | 0,35 |
| N Me | 29,3345 | 0,1353 | 23,8172 | 1,3769 | 4,68 | 0,08 |

* When R = N Me the substrate is

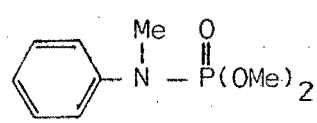


TABLE 2.3.

| No | R | Mean $k_{rel}$ | Std. Dev. | log (Mean $k_{rel}$) | ΔpKa |
|---|---|---|---|---|---|
| 1 | H | 1 | 0,0000 | 0 | 0 |
| 2 | 2 Me | 0,6912 | 0,0138 | -0,1604 | -0,15 |
| 3 | 3 Me | 1,0133 | 0,0002 | 0,0057 | 0,11 |
| 4 | 4 Me | 1,5895 | 0,0163 | 0,2013 | 0,48 |
| 5 | 3,4 diMe | 1,4560 | 0,1232 | 0,1632 | 0,57 |
| 6 | 2,6 diMe | 0,2771 | - | -0,5574 | -0,65 |
| 7 | 2 Et | 0,4374 | 0,0064 | -0,3591 | -0,30 |
| 8 | 4 Et | 1,4052 | 0,0019 | 0,1477 | 0,40 |
| 9 | 2t Bu | 1,0613 | - | 0,0258 | 0,43 |
| 10 | 4t Bu | 1,0948 | 0,0159 | 0,0393 | 0,35 |
| 11 | N Me | 23,8172 | - | 1,3769 | 0,08 |

of data may be determined. These values are listed together with the pKa values of the corresponding anilines in table 2.3. Using the values from table 2.3 (the reproducibility of which is very good, as indicated by the low standard deviations) we can correlate the relative reactivity with the difference in pKa values of the corresponding aniline. (The motivation for using pKa values for the anilines and not the phosphoramidates is given in the introduction). The correlation is represented graphically in Figure 2.2.

From this reactivity-basicity relationship a number of observations may be made. The group of phosphoramidates with meta and para substituents on the ring all correlate linearly with the corresponding relative basicities, as do the substrates with ortho substituents on the phenyl ring (with the exception of dimethyl N-(2-tert-butylphenyl) phosphoramidate which will be discussed later). The slopes of these two linear correlations are both positive but are however significantly different in that the slope for the ortho substituted phosphoramidates ($\beta$ = 0,8514; r = 0,961) is greater than that for the meta and para substituted phosphoramidates ($\beta$ = 0,3647; r = 0,905 when the points for 2*t* Bu and 4*t* Bu substrates are excluded. $\beta$ = 0,3544; r = 0,783 when only the point for the 2*t* Bu phosphoramidate is excluded from the linear regression). Both the N-methyl and ortho tert-butyl substrates deviate strongly from the reactivity-basicity relationship but reasons for this will be discussed seperately.

The analysis of the observed trends led us to the following conclusions. Firstly, the positive slopes for both the correlations are strong evidence that the kinetically reactive species is the N-protonated and not the O-protonated substrate. As mentioned in Chapter I, it is well known

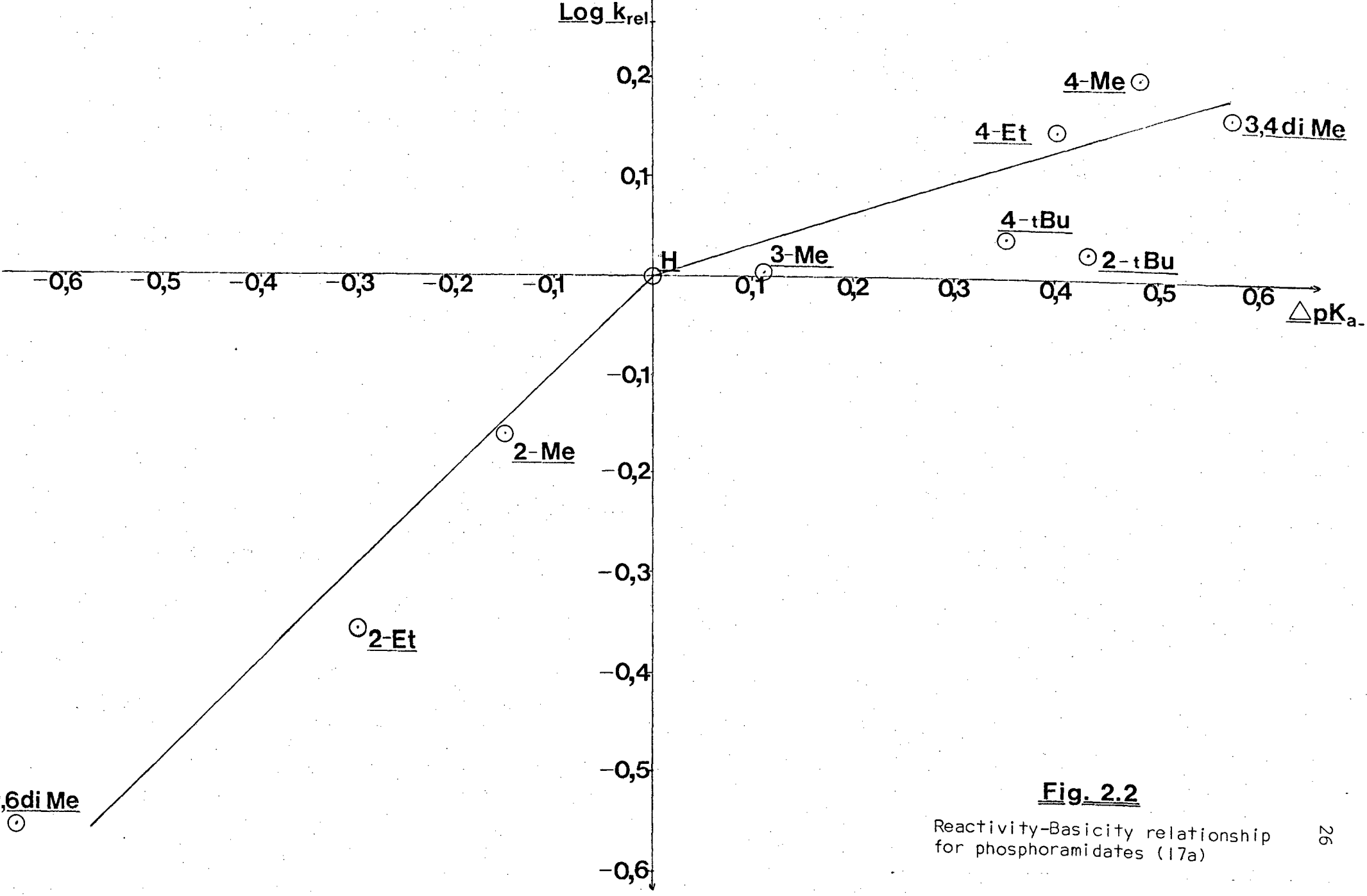



**Fig. 2.2**

Reactivity-Basicity relationship for phosphoramidates (17a)

that the acidic hydrolysis of carboxylic amides proceeds *via* the O-protonated species and similar studies to ours, on substituted benzanilides,[6,47] have afforded negative slopes. The sign of the slope of the log $k_\psi$ vs ΔpKa plot can be interpreted in the following way. The positive slope means that the electron-donating ring substituents accelerate the hydrolysis. Since the N-protenation of the phosphoric amide involves the change in the charge of nitrogen from zero to plus I, electron-donating substituents will strongly stabilize substrate's conjugate acid (see equation XVIII). In the substitution step itself, nitrogen atom decreases its charge from unity to a fraction of a positive charge (equation XVIII), so the substituent effect (operating in opposite direction) is of a smaller magnitude than on the preequilibrium step. In consequence, amides derived from more basic amines, exhibit higher reactivities in hydrolysis.

In the hydrolysis of carboxylic amides, the O-protonated form represents the kinetically important species:

$$R - C(O) - NHAr \overset{H^+}{\rightleftharpoons} [R - C(OH) - NHAr]^+$$

The protonation site (carbonyl oxygen) is removed much farther from the N-aromatic group, thus the protonation equilibrium is much less sensitive to the ring substituents. The rate-determining step on the other hand, involves the formation of the tetrahedral intermediate:

$$[R - C(OH) - NHAr]^+ + H_2O \xrightarrow{\text{slow}} R - \overset{OH}{\underset{+OH_2}{C}} - NHAr$$

and depends on the electrophilicity of a carbon centre. Since the O-protonated structure represents a highly conjugated system, electron-withdrawing substituents in group Ar will effectively increase the electrophilicity of the reaction center, hence increase the over-all rate of reaction.

Secondly, the change of slope in going from meta and para substituents to ortho substituents on the N-aromatic ring of the phosphoramidate might have suggested a change in mechanism from A1 to A2. Haake[1] in his work on phosphinanilides proposed that a decrease in the nucleophilicity of the aniline bonded to the phosphourus tended to cause the reaction mechanism to change from an A2 to an A1 type of mechanism and he proposed that it is possible to have a "merged A1-A2" type mechanism. This was supported by Koizumi[22] and Harger.[48] We initially believed that the change in the slope of the reactivity-basicity relationship in going from meta and para to the ortho substituted phosphoramidates was due to a similar effect. We considered the possibility that the relief of steric crowding due to the ortho substituents would tend to change the mechanism from A2 to A1.

## I.2 Determination of thermodynamic parameters and kinetic solvent isotope effects

In order to further investigate this proposed variation in mechanism with position of ring substituents in the phosphoramidates, we determined the Arrhenius parameters for the phosphoramidates listed in table 2.4 as well as the K.S.I.E. for a representative cross section of these substrates.

Arrhenius proposed that if the temperature range is not too great, the dependence of rate constants on temperature can usually be represented by the empirical equation XIX.[49]

$$k = Ae^{-\frac{Ea}{RT}} \qquad \text{(Eq. XIX)}$$

where A = pre-exponential frequency factor

Ea = Activation energy

$k$ = Gas const. = 8,314 J $K^{-1}$ $mole^{-1}$

T = Absolute temperature

Writing equation XIX in the form of a linear equation:

$$\ln k = -\frac{Ea}{RT} + \ln A \qquad \text{(Eq. XX)}$$

Thus the activation energy can be determined from the gradient of the linear plot of $\ln k_{\psi}$ against 1/T (see figure 2.3). The value for the Gibbs free energy of activation can be calculated from the relation

$$k = \frac{K}{h} Te^{-\frac{\Delta G^{\neq}}{RT}} \qquad \text{(Eq. XXI)}$$

where K/h = 2,083 x $10^{10}$ $sec^{-1}$ $deg^{-1}$ and the enthalpy of activation, $\Delta H^{\neq}$ and the entropy of activation $\Delta S^{\neq}$ can be calculated from equations XXII and XXIII respectively.

$$\Delta H^{\neq} = Ea - RT \qquad \text{(Eq. XXII)}$$

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$$

As mentioned in chapter I, the values of $\Delta S^{\neq}$ can provide insight as to whether the reaction proceeds *via* a uni- or bi-molecular mechanism.

All of the rate constants (with the exception of that for the dimethyl N-methyl N-phenyl phosphoramidate which was determined at temperatures between 20 and 40°C) were determined at five temperatures between 25 and 45°C and the same acidic dioxane-water solvent was used for all determinations. Again the linearity (r = 0,992 - 0,998) and reproducibility of results were good. For the K.S.I.E. determinations a solution of $D_2SO_4$ in 20% dioxane - $D_2O$ solution was used as solvent, the acidity of this solution being similar to that of the $H_2SO_4$ - dioxane - water solvent.

The results obtained are listed in table 2.4.

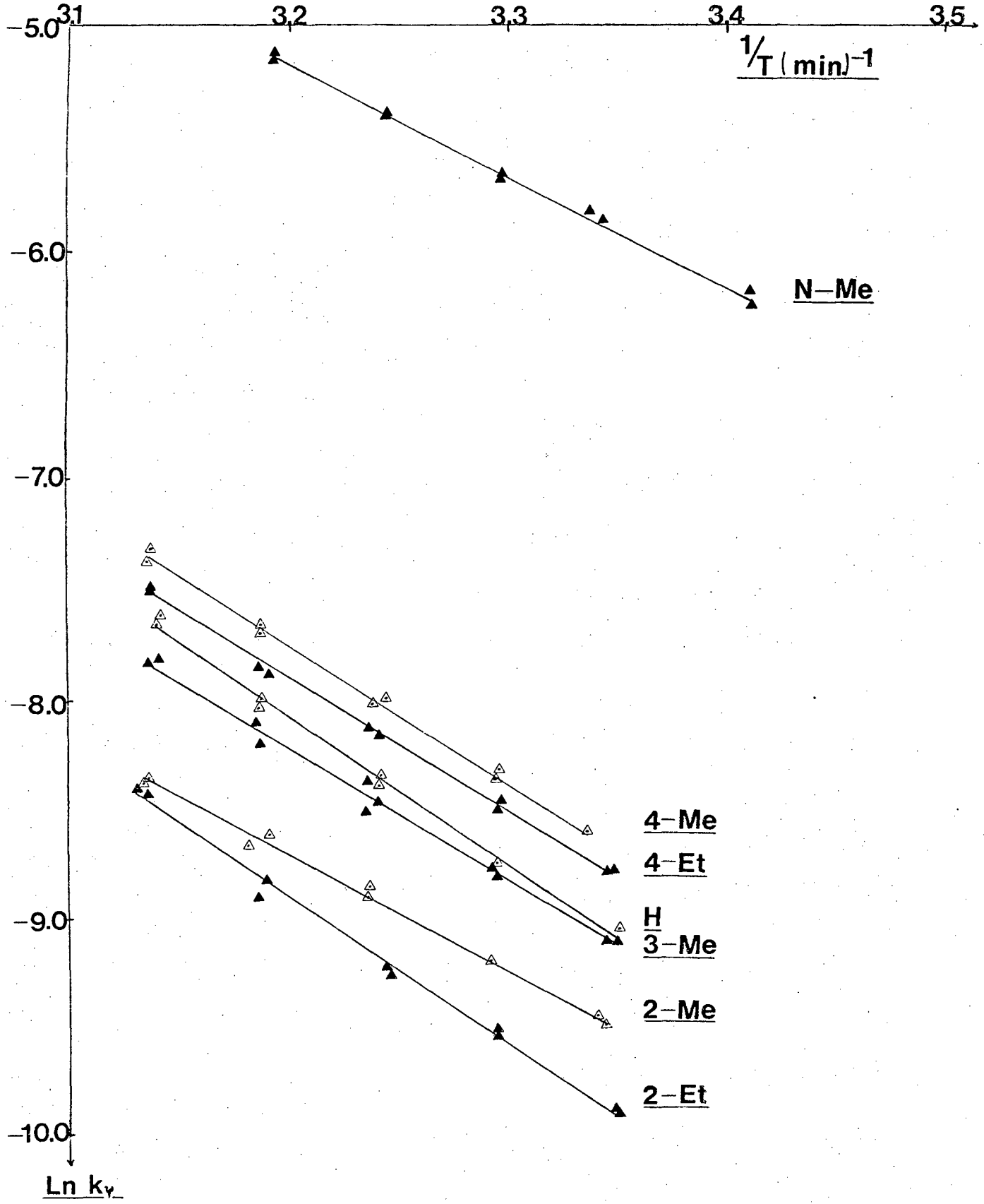



**Fig.2.3**

Temperature dependence
of rate constants

TABLE 2.4

| R | $E_a$ (kJ mole$^{-1}$) | lnA | r | $\Delta G^{\neq}_{298}$ (kJ mole$^{-1}$) | $\Delta H^{\neq}_{298}$ (kJ mole$^{-1}$) | $\Delta S^{\neq}_{298}$ (J mole$^{-1}$ K$^{-1}$) | $\frac{k_H}{k_D}$ |
|---|---|---|---|---|---|---|---|
| H | 56,32 | 13,83 | 0,9976 | 95,65 | 54,38 | -138,5 | 0,53 |
| 2 Me | 44,83 | 8,55 | 0,9973 | 96,62 | 42,36 | -182,0 | 0,48 |
| 3 Me | 50,32 | 11,15 | 0,9939 | 95,69 | 47,84 | -160,6 | - |
| 4 Me | 52,60 | 12,49 | 0,9975 | 94,63 | 55,08 | -132,7 | - |
| 2 Et | 56,66 | 12,89 | 0,9920 | 97,71 | 54,18 | -146,1 | - |
| 4 Et | 50,27 | 11,44 | 0,9970 | 94,91 | 47,72 | -158,4 | - |
| N-Me | 39,57 | 10,03 | 0,9931 | 87,69 | 37,09 | -169,8 | 0,55 |

Average values:

$\Delta S^{\neq}_{298}$ = 155,4 ± 17,5 J mole$^{-1}$ K$^{-1}$

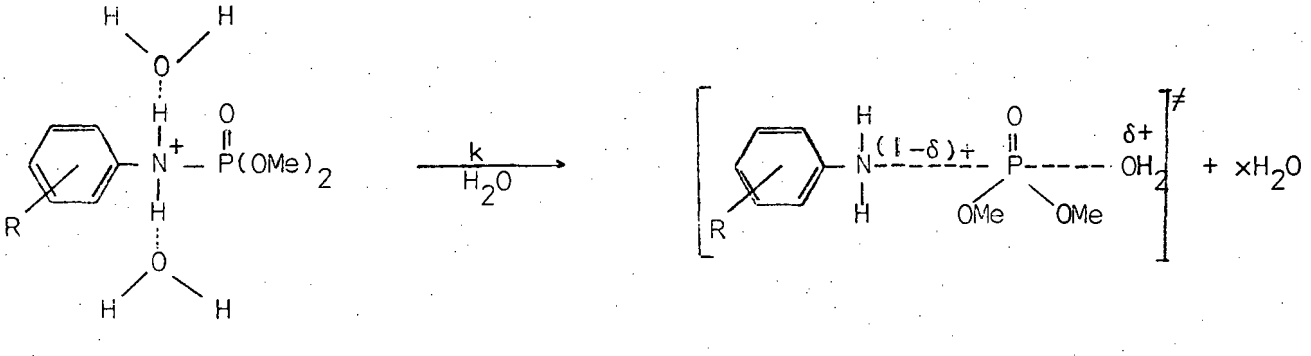
$k_H/k_D$ = 0,52 ± 0,04

## 2.2 Discussion

### 2.2.1 The reactivity-basicity relationship for phosphoramidates

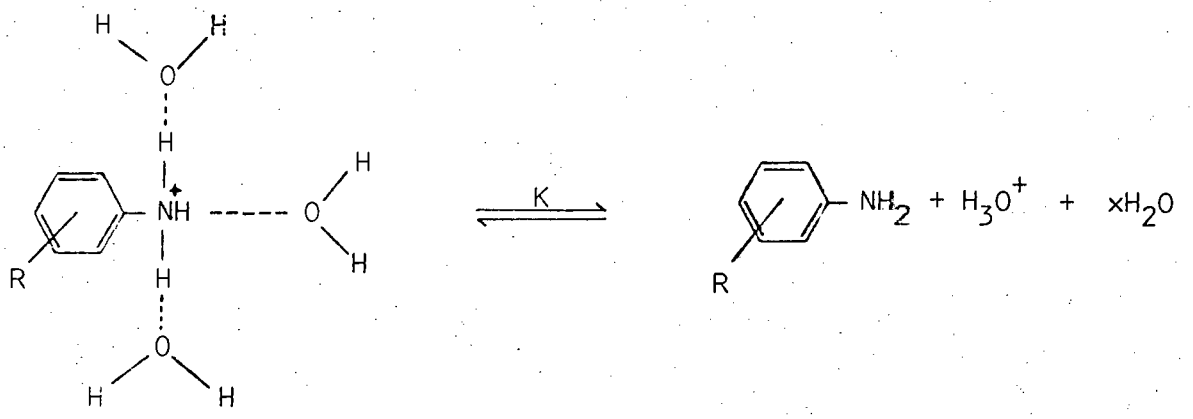
The most important observation to make from the results in table 2.4 is that the activation entropy is approximately constant for this group of phosphoramidates; irrespective of the position of the substituent on the phenyl ring and any variations observed are random in nature. All values are strongly negative indicating that the acidic hydrolysis of these substrates operates *via* an A2 type mechanism. Since there is no trend in the entropy values at all, the idea of a merged "A2-Al" or a change in mechanism from A2 to Al within this group of phosphoramidates, has to be rejected. The change in the slope of the reactivity - basicity relationship (figure 2.2) must therefore result from some other structural factor within the A2 acidic hydrolysis mechanism which is common to these substrates.

We propose that the position of the substituent on the phenyl ring of the phosphoramidates has a marked effect on the solvation of these compounds. Consider the following transition states for the meta and para substituted phosphoramidates (equation XIV) and the corresponding acid-base equilibrium for the anilinium ions (equation XV).



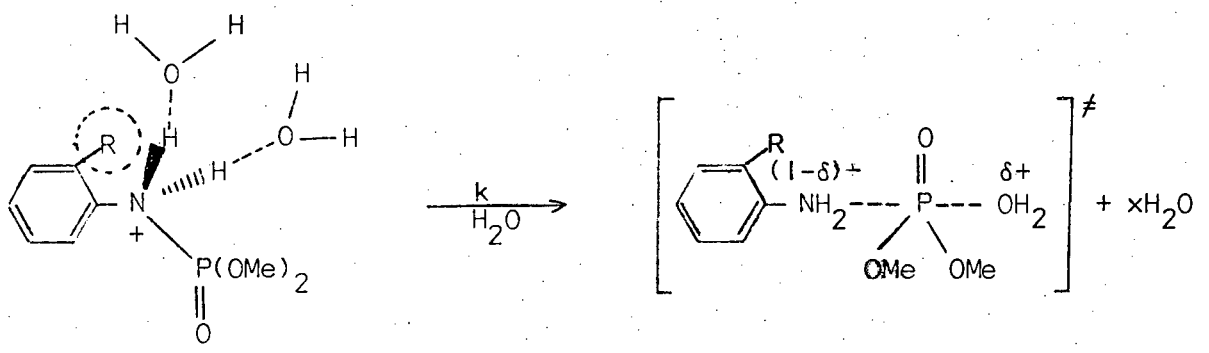

R = m or p substituent

(Equation XIV)

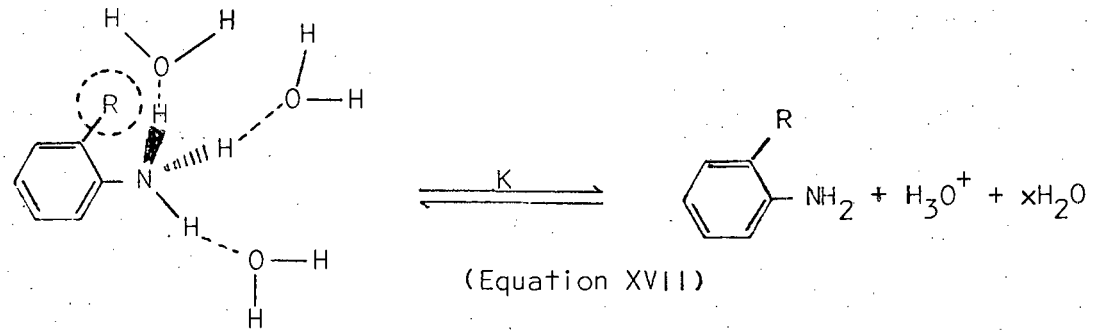


(Equation XV)

The major effects on $\Delta G^{\neq}$ for equation XIV and $\Delta G_o$ for equation XV are due to polar effects of the substituents R. These effects as well as the stabilisation of the protonated species due to solvation is similar for both the phosphoramidate and corresponding aniline and thus the reactivity of the phosphoramidate changes relatively slowly with change in basicity of the corresponding aniline. Consider now the ortho substituted phosphoramidates (equation XVI) and anilines (equation XVII).



(Equation XVI)



(Equation XVII)

Although the polar effects on $\Delta G^{\neq}$ and $\Delta G_o$ will be similar to those for the meta and para substituted phosphoramidates and anilines, a dramatic change in solvation can be expected around the charged nitrogen atom with the introduction of the substituent R in the ortho position.* The protonated species will thus not be stabilised by solvation to as great an extent as the substrates with meta or para substituents and the reactivity of these phosphoramidates in acidic media will be more sensitive to changes in basicity of the corresponding anilines. The slope of the reactivity - basicity relationship for ortho substituted phosphoramidates can therefore be expected to be much greater than that for the meta and para substrates. Moreover, the degree of steric inhibition to solvation will be different for the protonated amides (two hydrogen bonding centers) and for the anilinium ions (three hydrogen bonds possible). This new (steric) effect introduced is responsible for the fact that the linear free energy relationship between the log $k_{rel}$ and $\Delta$pKa values is not the same for all types of substitution (m, p, o) in the substrate molecule.

It is therefore very important to realise that the A2 type mechanism which is common for the acid catalysed hydrolysis of phosphoramidates, irrespective of the position of the substituents on the ring (see chapter I, equation VIII), is in fact a crude model since it ignores the effects of solvation completely. From our observations it is obvious that a change in the slope of the L.F.E.R. is <u>not</u> necessarily accompanied by a change in basic mechanism.

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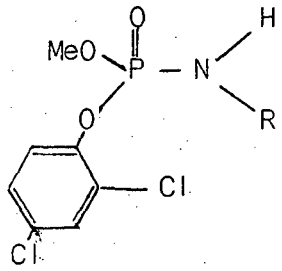
* Brown[50] was also aware that the $-NH_3^+$ group must be strongly associated with a sheath of water molecules in aqueous solutions but was uncertain as to what extent it was necessary to consider this sheath of water molecules in estimating the steric requirements of the protonated group.

In a literature survey, the activation parameters for the acidic hydrolysis of the P — N bond for a variety of substrates in various acidic media was found to compare favourably with the values which we obtained for our model.

In their study of the hydrolysis of (21) in a solution of 0,19 M HCl in 25% dioxane-water, Garrison and Boozer[4] obtained the results listed in table 2.5.




(21)

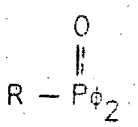
R = Me, Et, iPr, nBu, sec Bu or tert Bu.

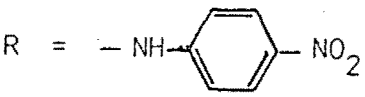
TABLE 2.5

| R | Ea (kJ mole$^{-1}$) | $\Delta G^{\neq}_{298}$ (kJ mole$^{-1}$) | $\Delta H^{\neq}_{298}$ (kJ mole$^{-1}$) | $\Delta S^{\neq}_{298}$ (J mole$^{-1}$K$^{-1}$) |
|---|---|---|---|---|
| Me | 43,51 | 79,50 | 41,00 | -129,7 |
| Et | 42,26 | 83,68 | 39,75 | -142,3 |
| Bu | 42,26 | 83,68 | 39,75 | -146,4 |
| iPr | 50,63 | 83,68 | 48,12 | -125,5 |
| sec Bu | 52,30 | 87,86 | 49,79 | -129,7 |
| *t*Bu | 55,23 | 92,05 | 52,72 | -129,7 |

Average $\Delta S^{\neq}_{298}$ = -133,9 ± 8,4 J mole$^{-1}$K$^{-1}$.

Haake studied the phosphinanilides (22)[1] and (23)[11] in a solution of 0,49 M $HClO_4$ in 10% dioxane-water and at pH 2,38 respectively. His findings are summarised in table 2.6.



R =  ----- (22)

$R = -NH_2$ ----- (23)

TABLE 2.6

| R | Ea (kJ $mole^{-1}$) | $\Delta G^{\neq}_{298}$ (kJ $mole^{-1}$) | $\Delta H^{\neq}_{298}$ kJ $mole^{-1}$) | $\Delta S^{\neq}_{298}$ (J $mole^{-1}K^{-1}$) |
|---|---|---|---|---|
| $O_2N$ NH- | 71,13 | 99,58 | 68,62 | -104,6 |
| $NH_2$ | - | 82,84 | 39,08 | -146,4 |

The average value for the activation entropy which we obtained in our study of the phosphoramidates listed in table 2.4 is -155,4 J $mole^{-1}K^{-1}$. The average value obtained by Garrison and Boozer for their phosphoramidates (21) is $\Delta S^{\neq}$ = -133,9 J $mole^{-1}K^{-1}$ and for the diphenylphosphinamide (23), Haake determined the value of $\Delta S^{\neq}$ as being -146,4 J $mole^{-1}K^{-1}$. It is therefore reasonable to postulate that a general and common transition state structure exists for these systems, *i.e.* even though the systems studied differ substantially, the configuration of the substrate and the solvation effects in the transition state for each system must be similar. One exception to this trend however, is the phosphinanilide (22) which has an entropy of activation of -104,6 J $mole^{-1}K^{-1}$, (considerably smaller in magnitude than the values obtained for all other

substrates). Haake postulated that this substrate was hydrolysed via an A1 type mechanism due to the weak nucleophilicity of the corresponding aniline (good leaving group). We believe, however, that the mechanism is not pure A1 but only tends towards an A1 type mechanism with decreasing nucleophilicity of the leaving group, thereby supporting his proposed "merged A1-A2" mechanism. The values for the kinetic solvent isotope effect for the unsubstituted, 2 methyl and N-methyl phosphoramidates are all similar ($k_H/k_D$ = 0,52 ± 0,04) indicating that these compounds are hydrolysed via a similar mechanism. The ratio between the rate constants for the acidic hydrolysis of these phosphoramidates in $H_2O$ and $D_2O$ is less than unity and this is characteristic of an acid catalysed reaction with a reversible proton transfer prior to the rate determining step.[42] This confirms the general hydrolysis mechanism for the phosphoramidates studied as being:

$$S + H^+ \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} SH^+ \xrightarrow[\text{slow}]{k_2} \text{products}$$

2.2.2 Substrates deviating from the reactivity-basicity relationship

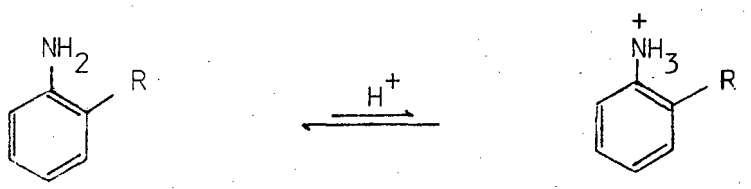
(a) Dimethyl N-(2*t* butylphenyl) phosphoramidate

There seems to be some uncertainty in the determination of the basicity of the 2*t* butylaniline since two apparently contradictory values have been reported in the literature.[46] These are:

(a) pKa = 5,03 which implies that the 2*t* butylaniline is a stronger base than aniline;

(b) pKa = 2,78 which implies that it is a weaker base than aniline.

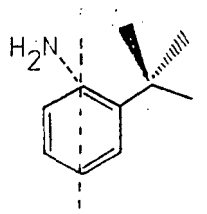
Because of this uncertainty we did not attach too much importance to the position of this point in figure 2.2 even though the rate constants obtained for the hydrolysis of the corresponding phosphoramidate were reproducible. We do however prefer to consider 2*t* butylaniline as being a stronger base than aniline for the following reason: We believe that the anilines (24) are weaker bases than the unsubstituted aniline since the substituent in the ortho position hinders solvation of the conjugate acid (25).




R = Me, Et, 2,6 diMe

(24) (25)

The ortho *t* butylaniline would be expected to behave in a similar manner making it a weaker base than aniline but it is highly possible that since it is such a bulky group it tends to force the adjacent $-NH_2-$ group of the aniline (26) out of the plane of the ring, hence reduced the conjugation with the phenyl ring. This would tend to give the $-NH_2$ group more aliphatic character and thus increase the basicity of the ortho *t* butylaniline relative to aniline. The possibility of such a steric inhibition of resonance has been suggested by H.C. Brown.[51]



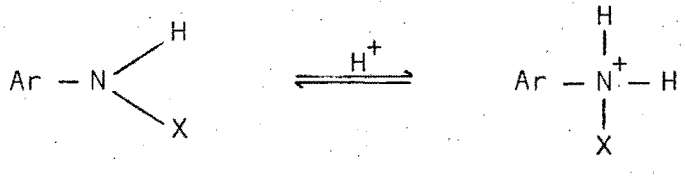

(26)

The position of the point for the 2*t* butyl substituted phosphoramidate in the reactivity-basicity relationship (figure 2.2) would seem to support this argument.

Thompson[52] found that while 2 methyl aniline was less basic than aniline the N,N-dimethyl 2 methylaniline was more basic than N,N-dimethylaniline. We believe that this is also due to the more severe steric crowding pushing the nitrogen atom out of conjugation with the phenyl ring with the same effect as mentioned above.

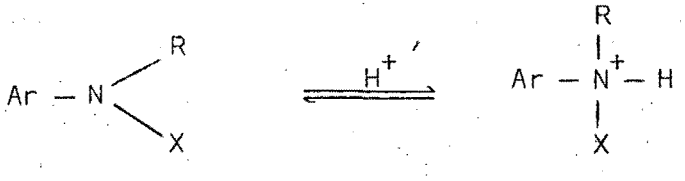
(b) Dimethyl-N-methyl-N-phenyl phosphoramidate

Tertiary substrate, dimethyl N-methyl-N-phenyl phosphoramidates (Table 2.3, No. II) deviates strongly from the log $k_{rel}$ - ΔpKa relationship in a sense that its reactivity is much higher ($k_{rel}$ = 24-29) than it could have been expected from the basicity of N-methyl aniline (pKa = 4,68). Such a result can be easily explained in terms of the behaviour of weak bases in non-ideal solutions and indicate again the importance of solvation effects in hydrolysis of phosphoramidates. Since the reaction medium is far from ideal (*ca.* 3,5 M $H_2SO_4$ in aqueous dioxane), its acidity has to be described by the appropriate acidity function. Protonation equilibrium for all the secondary amides studied can be compared with the protonation of secondary amines, as far as the number of hydrogen bonding centers (N-H bonds) involved in a conjugate acid:



(Eq.XXVIII

For the tertiary substrate (II), the protonation behaviour has to be compared with that for tertiary amines:



(Eq. XXIX)

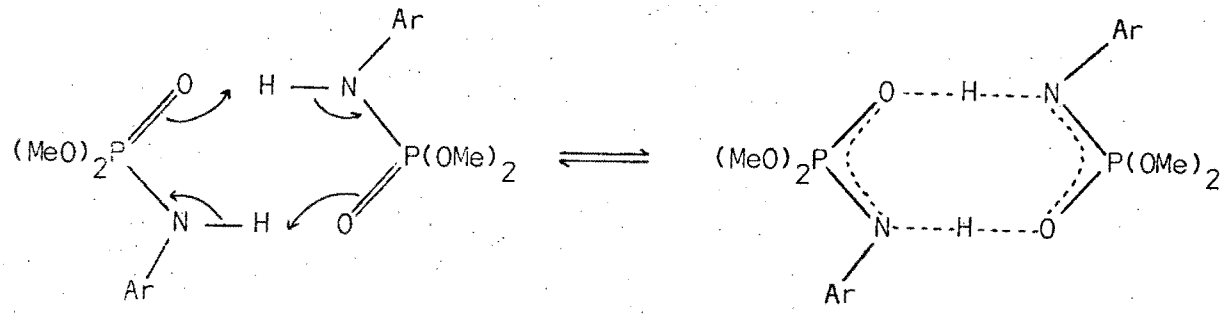
In concentrated acids (beyond the pH range) protonation equilibria (XXVIII) and (XXIX) are described by two different acidity functions.[53] At the same concentration of acid equilibrium (XXIX) will be shifted more to the right than (XXVIII) because the conjugate acid involved has lower hydration requirements (one $N^+-H$ group) than the analogous species in equation XXVIII (two $N^+-H$ groups). In consequence, in strongly acidic medium amidate (II) will be protonated (relatively to the secondary substrate $(MeO)_2P(O)$-NHPh) to a greater extent than it could be expected from the difference in the pKa values of the corresponding anilines (determined in the diluted, aqueous solutions). The greater reactivity of compound (II) results therefore mainly from the greater (relative) concentration of its reactive, protonated form (equation XVIII).

Such a strong dependence of the hydrolytic reactivity to the hydrating properties of the reaction medium remains in agreement with the postulated N-protonated form of a substrate in the hydrolysis scheme. The O-protonated form of a phosphoramidate should be characterized by a significant charge delocalization, hence lower sensitivity to the hydrogen bonding properties of the reaction solution.

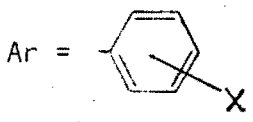
## 2.3 INFRARED DETERMINATIONS

The formation of dimers and polymers by carboxylic amides in non polar solvents has long been known from cryoscopic measurements, behaviour as solvents, high melting and boiling points *etc.*[54] Buswell[55] found that while ordinary carboxylic amides show a strong tendency towards association, the monosubstituted amides show a smaller tendency and the disubstituted amides do not associate at all. He found that the unsubstituted carboxylic amides tended to form polymers of indefinite molecular weight while there was a tendency for a large percentage of the monosubstituted amides to associate in the form of dimers.

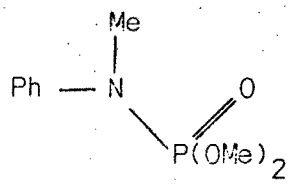
In order to study similar effects in the phosphoramidates the P=O stretching frequencies, $\nu_{po}$ (str) were measured for the dimethyl N-arylphosphoramidates (17a and b) in nujol and in dilute solutions (ca. $2,5 \times 10^{-3}$ M) in the nonpolar solvents, benzene and $CCl_4$. For the parent anilide (27 (Ar = Ph)) $\nu_{po}$ (nujol) was 1229 $cm^{-1}$ which is much lower than the "normal" value of 1270 - 1280 $cm^{-1}$ for the free phosphoryl group. The PO str. absorption peak in nujol for the N-methyl derivative (28), which is not capable of self association, appears at 1275 $cm^{-1}$ and the difference of 46 $cm^{-1}$ can therefore be taken as a measure of the effect of hydrogen bonding on the stretching frequency of the phosphoryl group. The amide function in (27) can serve both as a donor and an acceptor of the hydrogen bond which results in the formation of polymeric aggregates or symmetrical dimeric structures (27a). The presence of the dimeric structure (27a) has been demonstrated by x-ray analysis for the derivatives (27, Ar = 4 $MeOC_6H_4$; Ph).[56,57] Internally stabilised dimers (27a) are still relatively low molecular species (M.M. = 400-500 gr/mole) and in solvents which do not offer compensating solvent-solute hydrogen bonding



(27) (27a)



(EQUATION XXX)



(28)

(*e.g.* benzene or $CCl_4$) the dissociation (27a) $\rightleftharpoons$ 2(27) may not be far advanced. Harger[58] demonstrated that chiral phosphinamides form diastereomeric dimers (involving the pair of the O — H --- O = P and N — H --- S = P hydrogen bonds) with optically active phosphinothioic acids in chloroform. It is reasonable therefore to expect that, at least for some of the anilides (27) it is not possible to determine the $\nu_{str}$ value for the "free" phosphoryl group even at high dilution. Table 2.7 gives the $\nu_{po}$ values determined for the phosphoramidates (17a & b).

It is obvious that for most of the anilides studied, hydrogen bonding effects do not disappear when the substrate is transferred from the solid state (nujol mull) to the dilute solution in benzene or $CCl_4$. In the substrates B to K (table 2.7), substituted only by alkyl groups,

TABLE 2.7

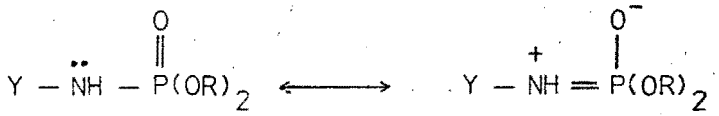
| | X in (27) | σx[58] | In nujol | | In benzene[a] | | In $CCl_4$[a] | | $\nu_{(CCl_4)} - \nu_{(nujol)}$ |
|---|---|---|---|---|---|---|---|---|---|
| | | | νpo | Δνpo[b] | νpo | Δνpo | νpo | Δνpo | |
| A | H | - | 1229,0 | 0,0 | 1228,0 | 0,0 | 1228,5 | 0,0 | -0,5 |
| B | 2-Me | - | 1238,5 | +9,5 | 1242,0 | +14,0 | 1249,5 | +21,0 | +11,0 |
| C | 3-Me | - | 1235,0 | +6,0 | 1235,0 | + 7,0 | 1238,0 | + 9,5 | + 3,0 |
| D | 4-Me | -0,17 | 1231,5 | +2,5 | 1228,5 | + 0,5 | 1228,0 | - 0,5 | - 3,5 |
| E | 3,4-diMe | - | 1237,0 | +8,0 | 1235,0 | + 7,0 | 1225,0 | +26,5 | +18,0 |
| F | 2,6-diMe | - | 1237 | +8,0 | 1272,5 | +44,5 | 1273,0 | +44,5 | +36,0 |
| G | 2-Et | - | 1242 | +13,0 | 1237,0 | + 9,0 | 1266,0 | +37,5 | +24,0 |
| H | 4-Et | - | 1227,5 | - 1,5 | 1218,5 | - 9,5 | 1218,0 | -10,5 | - 9,5 |
| I | 4*n*-Bu | - | 1232 | + 3,0 | 1227,0 | - 1,0 | 1227,5 | - 1,0 | - 4,5 |
| J | 4*t*-Bu | - | 1235,5 | + 6,5 | 1229,0 | + 1,0 | 1254,0 | +25,5 | +18,5 |
| K | 2*t*-Bu | - | c | - | 1251,5 | +23,5 | 1275,0 | +46,5 | - |
| L | 4-Ph | -0,01 | 1225,5 | - 3,5 | 1227,0 | - 1,0 | 1227,5 | - 1,0 | + 2,0 |
| M | 3-F | - | 1233,0 | + 4,0 | 1235,5 | + 7,5 | 1235,5 | + 7,0 | + 2,5 |
| N | 4-F | + 0,06 | 1228,5 | - 0,5 | 1225,5 | + 2,5 | 1229,0 | + 0,5 | + 0,5 |
| O | 3-OMe | - | 1233,5 | + 4,5 | 1236,0 | + 8,0 | 1235,5 | + 7,0 | + 2,0 |
| P | 4-OMe | -0,27 | 1224,0 | - 5,0 | 1225,0 | - 3,0 | 1225,0 | - 3,5 | + 1,0 |
| Q | 3-$NO_2$ | +0,71 | 1236,0 | + 7,0 | 1234,0 | + 6,0 | 1233,5 | + 5,0 | - 2,5 |
| R | 4-$NO_2$ | +0,78 | 1231,5 | + 2,5 | 1234,0 | + 6,0 | 1234,6 | + 6,0 | + 3,0 |
| S | 4-$NMe_2$ | -0,83 | 1218,0 | -11,0 | 1219,0 | - 9,0 | 1217,0 | -11,5 | - 1,0 |

a 0,1 % solution
b $\Delta\nu po = \nu po(x) - \nu po(H)$
c No homogenous mull could be prepared.

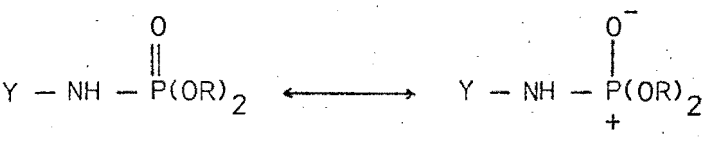
electronic effects should be similar and differ only very slightly from the unsubstituted compound A. The observed differences in the $_{po}$ values can therefore be interpreted primarily in terms of the degree of hydrogen bonding. For the parent anilide, A, the $^{po}$ value of 1229 $cm^{-1}$ remains virtually unchanged upon dilution. We postulate therefore that A exists in solution predominantly as a dimer (27a), and solvation effects (by benzene or $CCl_4$) involve mainly the N-aromatic and P-methoxy groups. It seems that the same is true for all meta and para ring substituted derivatives studied (with the exception of the p-t-Bu derivative), as indicated by the low values of the corresponding $\nu_{(CCl_4)} - \nu_{(nujol)}$ shifts in table 2.7. The average value of this shift for compounds (A), (C), (D), (H), (I) and (L) to (S) is -0,6 (±3,6) $cm^{-1}$, much in contrast to the corresponding value of *ca.* + 60 $cm^{-1}$ observed for carboxylic anilides.[59] However, for all compounds containing alkyl substituents in the ortho position(s) significant shift to the higher values of $\nu_{po}$ is observed upon dilution. For substrates (B), (F) and (G), $\nu_{(CCl_4)} - \nu_{(nujol)}$ = + 11 to + 36 $cm^{-1}$; in fact we believe that the N-(2,6 dimethylphenyl), (F), and the N-(2 tert-butylphenyl), (I), derivatives are virtually free of any molecular association in solution, since for these compounds, $\nu_{po}$ attains the "normal" value observed for the hydrogen bonding free N-methyl-N-phenylamidate (28). Since the dimeric structure (27a) requires the syn orientation of the P=O and N-H groups, some conformational restrictions are introduced to this system. Molecular (Dreiding) models of (27a) demonstrate that the introduction of a single methyl group at the ortho position of the ring results in further significant restrictions to the free rotation around the N-C (aromatic) and P-OMe bonds. It can be concluded therefore that the dimerization constant for the equilibrium 2(27)$\rightleftharpoons$(27a) is large even at low substrate concentrations (due to the enthalpy of the two hydrogen bonds formed) unless the entropy factors resulting from the steric crowding at the

N-aryl substituent counterbalance these effects. It has been reported[60] that the dimerization of phosphinic acids $R_2PO_2H$ is affected by the steric bulk of groups R, and for R = tert-Bu, the dimeric structure involving two P and four O atoms is forced out of the plane. Data in table 2.7 indicates that steric effects also operate in amides substituted by bulky groups in the para position (J) or in polysubstituted systems (E). Since the formation of the hydrogen bonded structure decreases the bond order of the phosphoryl group (equation XXX), the comparison of the $\nu_{po}$ values for a series of isomeric amides can provide information about the steric effects upon the equilibrium (Equation XXX). In a series of four monomethyl derivatives of (A), the expected steric hindrance to self association should increase in the order of para, meta, ortho substitution and in the N-methyl derivative the hydrogen bonding should be completely eliminated. The values of $\nu_{po}$ for the methyl derivatives of (27) measured both in nujol and in $CCl_4$ increase in the expected order (D) < (C) < (B) << (28).

The formal analogy between carboxylic and phosphoric amides suggests that the latter can also be described in terms of the resonance effect of the amidate group.

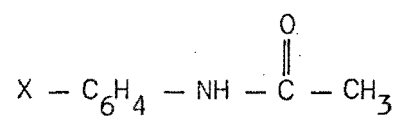


However it is accepted[41] that in the phosphoryl compounds the conjugation involving the PO group and adjacent ligands is less extensive than in carbonyl structures, in fact it might only be limited to the phosphoryl group.



In such a case the response of the PO bond order (and the $\nu_{po}$ value) to the structural variations Y should be less pronounced than the effect of N-substitution in carboxylic amides. As we demonstrated above, almost all of substrates (27) exist, even in dilute solutions, as (at least partly) self-associated species. It seems however that the substituent effects upon the $\nu_{po}$ in (27) can be assessed in terms of the linear free energy relationship regardless of whether the substrate exists as a monomer (27) or mainly as a dimeric structure (27a).

Since any polar effects of substituents introduced to the aromatic moiety Ar would change the hydrogen bonding donor property of the phosphoryl oxygen and the acceptor property of the NH group in opposite directions, the nett effect upon the bonding order of the PO group should be approximately similar in (27) and (27a). We have correlated the shifts $\Delta\nu_{po}$ (relative to the unsubstituted anilide) with Hammett's $\sigma$ constants[61] for a few representative amidates (27) substituted with electron-withdrawing and electron-donating groups. Similar shifts $\Delta\nu_{CO}$[62] for substituted acetanilides (29) are listed in table 2.8.



(29)

The correlation is of similar linearity (r = 0,985) to that observed for the acetanilides (29, r = 0,980) and the corresponding plots are presented in figure 2.4. For the acetanilides (29) the slope of the plot of $\Delta\nu_{CO}$ vs $\sigma$ is 20 $cm^{-1}$; phosphoramidates (27) show greatly reduced sensitivity to the substituent effects of groups X (slope = 10 $cm^{-1}$). Although this L.F.E.R. has to be considered as semiquantitative because of the hydrogen bonding effects, and probably the mass effects (for both plots of $\Delta\nu$ vs $\sigma$ a negative value for the intercept is obtained),

TABLE 2.8

| X in (29) | $\sigma_x$ [58] | $\nu_{CO}(CCl_4)$ [59] | $\Delta\nu_{CO}$ |
|---|---|---|---|
| H | 0,00 | 1705 | 0,0 |
| 3-Me | -0,07 | 1704 | -1,0 |
| 4-Me | -0,17 | 1700 | -5,0 |
| 3,4-diMe | -0,24 | 1700 | -5,0 |
| 3-OMe | +0,12 | 1707 | +2,0 |
| 4-OMe | -0,27 | 1696 | -9,0 |
| 3-Cl | +0,37 | 1713 | +8,0 |
| 4-Cl | +0,23 | 1710 | +5,0 |
| 3-Br | +0,39 | 1712 | +7,0 |
| 4-Br | +0,23 | 1710 | +5,0 |
| $3\text{-}NO_2$ | +0,71 | 1716 | +11,0 |
| $4\text{-}NO_2$ | +0,78 | 1720 | +15,0 |

figure 2.4 demonstrates the undoubtedly lower sensitivity of the phosphoramidate function to the molecular polar effects, relative to the carboxyamide system. If we assume that in the acetanilide system (29) the relative contributions of the inductive and resonance effects upon the CO group parallel those in acetophenones,[30,31] the values of $\rho_I$ and $\rho_R$ for (29) should be *ca.* + 10 each. There is no reason to expect that the inductive effects of the substituents X in amides (29) and (27) should be much different; the distance between X and CO (or PO) groups is the same and the effects are transmitted through the same molecular framework. It follows therefore that in the phosphoric anilides (27) the resonance contribution of X is negligible, *i.e.* the phosphoramidate group $P(O)NR_2$ is not the extensively conjugated system. This conclusion is in full agreement with our results derived from the $^{13}C$ NMR study,[12] as well as with the recent work[63] on the $^{15}N$ NMR spectroscopy of N-aryl-phosphoramidates.

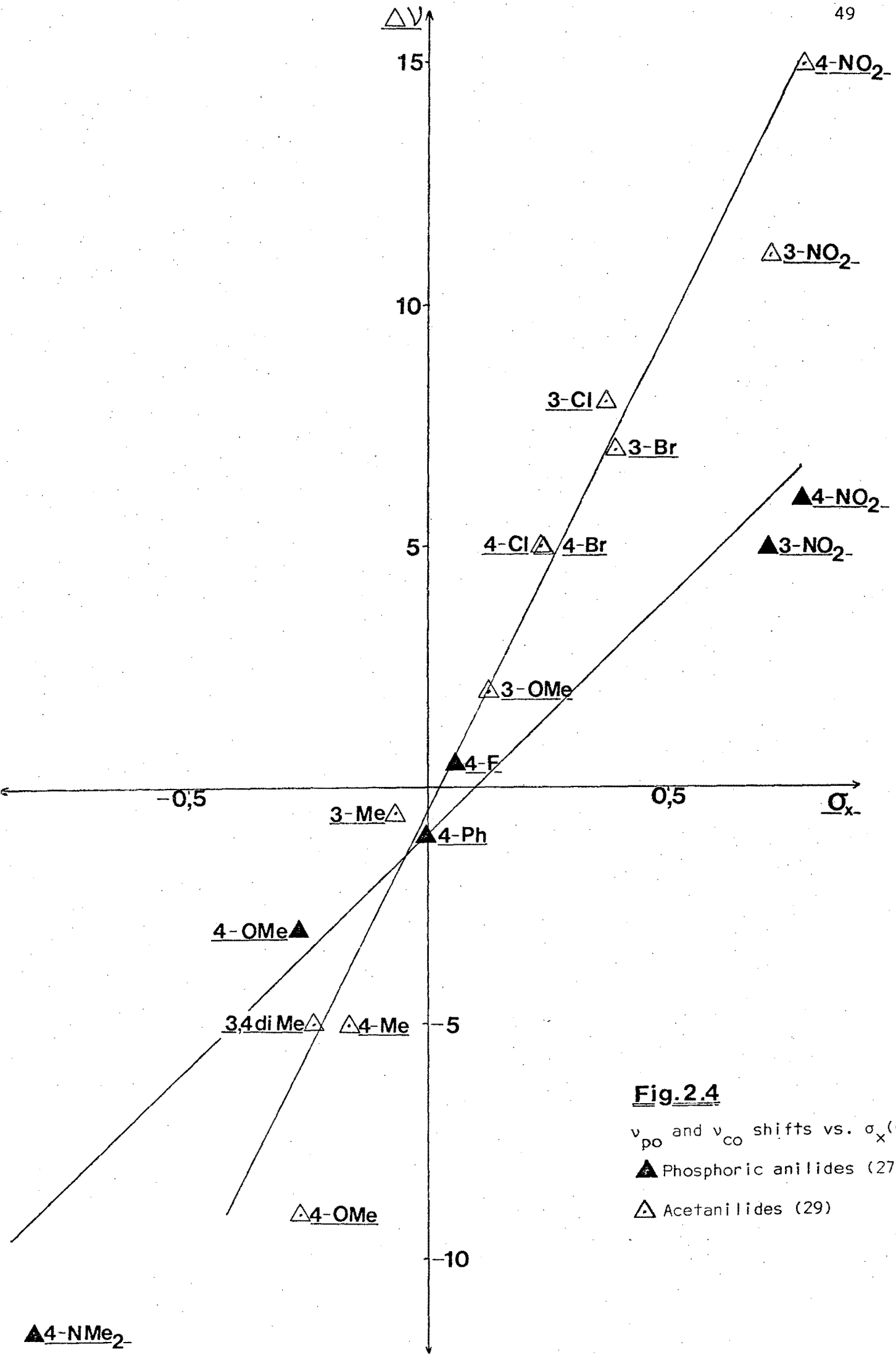



**Fig.2.4**

$\nu_{po}$ and $\nu_{co}$ shifts vs. $\sigma_x$(CCl

▲ Phosphoric anilides (27)

△ Acetanilides (29)

# CHAPTER THREE

# EXPERIMENTAL

# 3. EXPERIMENTAL

## 3.1 General

Solvents used were BDH Anala R reagents and all water was glass distilled. Benzene was dried over sodium wire while diethylether was distilled from lithium aluminium hydride before use. The anilines were supplied by BDH or Merck and were all distilled or recrystallised prior to use. Dimethylphosphorochloridate was prepared in the laboratory according to the procedure described by Fiszer *et al*[64] and was distilled prior to use in syntheses.

Proton magnetic resonance spectra were recorded in deuterated chloroform with tetramethylsilane as internal reference on a 100 MHz Varian XL 100 spectrometer. A Fischer-Johns melting point apparatus was used to determine melting points of products. Aluminium backed silica gel 60 $F_{254}$ plates were used for thin layer chromatography and column chromatography was carried out with Merck silica gel 60 packed in the solvent used for elution. Kinetic runs were performed on a Beckman UV 5260 spectrophotometer and water at constant temperature (±0,2°C) was circulated through the sample cell compartment by means of a Haake constant temperature circulator. Quartz cuvettes of 1 cm path length were used for both reference and sample. Infrared spectra were run between 1350 and 1150 $cm^{-1}$ on a Perkin-Elmer 180 spectrophotometer. An obscissa expansion of 5 $cm^{-1}$ per cm, was used and values of $\nu_{po}$ are accurate to within ±0,5 $cm^{-1}$. The nujol mulls were run of CsBr plates whereas the benzene and $CCl_4$ solutions were run in solution cells with NaCl windows and a path length of 0,1 mm. Microanalyses were performed at the Department of Organic Chemistry at the University of Cape Town.

## 3.2 Stock solutions for spectrophotometric determinations

### A. 20% Dioxane - water solution

20 ml of 1,4 dioxane (BDH Anala R reagent) was made up to 100 ml with glass distilled water for every 100 ml of stock solution needed.

### B. Acidified dioxane - water solution

Concentrated sulphuric acid (35 gm) (analytical reagent from Laboratory and Scientific Equipment Company (Pty.) Ltd.) was mixed with 20% dioxane - water solution and made up to 100 ml with the same dioxane - water solution. The acid concentration in this stock solution was determined using standardised sodium hydroxide with phenolphthalein indicator.

### C. Sample solutions

Approximately $1,0 \times 10^{-4}$ mole of the phosphoramidate was accurately weighed in a 10 ml volumetric flask and 20% dioxane - water solution added to make up 10 ml of sample stock.

### D. 20% Dioxane - deuterium oxide solution

1,4 Dioxane (8 ml) was made up to 40 ml with deuterium oxide (Merck, Sharp and Dohme, Canada - Minimum isotopic purity = 99,7 atom % D).

### E. 3,5 Molar deuterium sulphate - dioxane - deuterium oxide solution

Deuterium sulphate (9,02 gm) (MSD, Canada. 96% in $D_2O$ - minimum isotopic purity = 99 atom % D) was carefully added to 15 ml 20% deuterium oxide - dioxane solution and made up to 25 ml with the deuterium oxide - dioxane solution.

## 3.3 Sample preparation for UV spectrophotometric determinations

A. For determinations of absorbance *vs* wavelength of the phosphoramidates, the sample was prepared by adding 0,4 ml of the sample stock solution to 3,6 ml of plain 20% dioxane - water solution. The reference cell contained only 20% dioxane - water solution.

B. For the determination of the decrease in absorbance at a fixed wavelength with time, for rate studies, the sample was prepared by adding 0,4 ml of the sample stock solution to 3,6 ml of the acidified dioxane - water solution which had been pre-heated to the temperature at which the UV study was to be carried out. The reference sample was prepared by adding 0,4 ml of plain 20% dioxane - water solution to 3,6 ml of the acidified dioxane - water solution. The initial time t = 0 minutes was taken as the time at which the stock solution was added to the acidic dioxane - water solution. Recording of the decrease in absorbance with time could generally only be started a few minutes after the addition but this delay was taken into consideration when the rate constants were calculated.

## 3.4 Validity of Beers Law for phosphoramidates

Since our kinetic studies were to be performed with the aid of a UV spectrophotometer, it was important to know whether the phosphoramidates obeyed Beers law over the concentration range to be used in the studies.

Solutions containing varying concentrations of dimethyl N-phenylphosphoramidate in 20% dioxane - water were prepared and the absorbances measured at 273 mμ wavelength.

Table 3.1

| Phosphoramidate conc. (Mole/lit) (C) | Absorbance (A) |
|---|---|
| $3,5397 \times 10^{-3}$ | 2,923 |
| $1,7698 \times 10^{-3}$ | 1,482 |
| $0,8849 \times 10^{-3}$ | 0,754 |
| $0,8849 \times 10^{-4}$ | 0,082 |
| $0,8849 \times 10^{-5}$ | 0,008 |

From Beers-Lambert law, $A = \varepsilon C l$

Since 1 cm cuvettes were used, $A = \varepsilon C$.

The values for the plot of A against c for dimethyl N-phenyl phosphoramidate in the concentrations given in Table 3.1 were used in a linear regression and the following values obtained:

Gradient = molecular extinction coefficient, $\varepsilon$ = 824,7 litre $mole^{-1}$ $cm^{-1}$.

Y axis intercept = 0,0121.

Correlation coefficient = 0,9999.

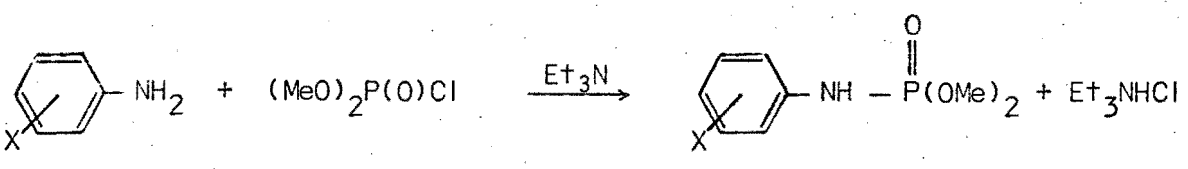
From these results it can be seen that the plot of absorbance against concentration is linear and thus the Beer-Lambert law is obeyed over the above concentration range of dimethyl N-phenyl phosphoramidate.

Since alkyl substituents on the phenyl ring of dimethyl N-phenyl phosphoramidate do not alter spectrophotometric properties to any significant degree, the Beer-Lambert law has been assumed to apply for the dimethyl N-(alkyl substituted) phenyl phosphoramidates as well.

## 3.5 Methods of synthesis

### 3.5.1 General procedure used for the synthesis of dimethyl N-(substituted phenyl) phosphoramidates

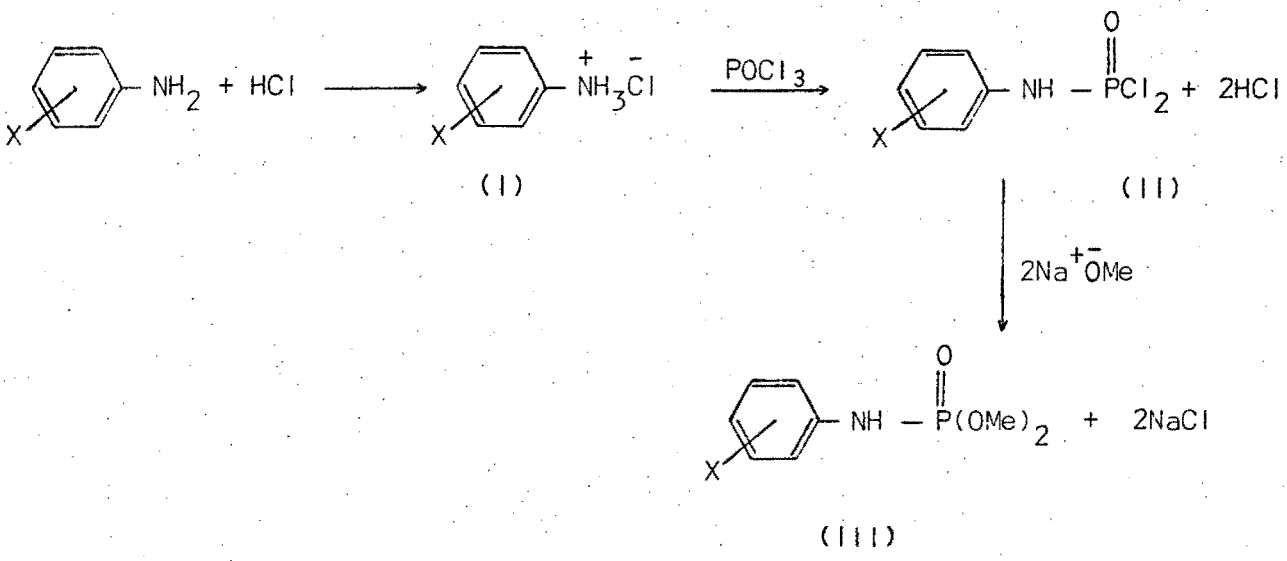
Reaction:




Freshly distilled dimethylphosphorochloridate (0,035 mole) in 20 ml of dry benzene was added dropwise to a stirred solution of the freshly distilled aniline (0,035 mole) and triethylamine (0,040 mole) in 80 ml dry benzene. Moisture was excluded from the reaction mixture and the temperature was kept below 15°C during the addition. The mixture was stirred for a further 3-5 hours at room temperature and allowed to stand overnight. The triethylaminehydrochloride was filtered off and washed with dry benzene, the filtrates combined, washed with distilled water, dried over anhydrous sodium sulphate and the solvent removed under vacuum. An oil from which the product crystallised on standing was generally obtained. The crystals were filtered, washed with a small quantity of petroleum ether (60-90°C) and purified as indicated in the section: "Data on compounds prepared using method 3.5.1". All crystals were dried in vacuo over silica gel before analyses and melting points were determined.

3.5.2 General procedure used for the synthesis of dimethyl N (substituted phenyl) phosphoramidates where the ring substituent is electron withdrawing

Reaction:




(I) (II) (III)

(a) Synthesis of the aniline hydrochoride (I)

Dry HCl gas was passed through a solution of freshly distilled substituted aniline (0,065 mole) in 200 ml of dry diethylether. When the formation of precipitate was complete, the salt was filtered, washed with a small quantity of dry diethylether and dried in vacuo over silica gel. The product was used for the following step without further purification.

(b) Synthesis of N (substituted phenyl) phosphorus oxychloride (II)

The aniline hydrochloride (0,02 mole) was added to an excess of freshly distilled $POCl_3$ and the mixture stirred and refluxed gently under anhydrous conditions. Once the solid hydrochloride had dissolved, the solution was refluxed for a further 5 hours and left at room temperature overnight. The excess $POCl_3$ was removed under vacuum to leave a pale yellow oil which was used in the next stage without further purification.

(c) Synthesis of dimethyl N (substituted phenyl) phosphoramidate (III)

The crude aryl-phosphorodichloridate (approx. 0,025 mole) in 25 ml dry diethylether was added dropwise to a stirred solution of sodium metal (0,10 mole) dissolved in 200 ml absolute methanol and the temperature kept below 20°C during addition. The pH of the mixture was checked regularly but it remained alkaline throughout the addition. The mixture was stirred overnight at room temperature, the precipitate filtered off and the solvent removed from the filtrate under reduced pressure. The resulting solid was dissolved in benzene and this solution washed with water, dried over anhydrous sodium sulphate and the solvent removed.

Crude products were purified as indicated in "Data on compounds prepared using method 3.5.2". All crystals were dried *in vacuo* over silica gel before analyses and melting points were determined.

## 3.6 Product Data

### 3.6.1 Data on compounds prepared using method 3.5.1

#### (a) Dimethyl N (phenyl) phosphoramidate

Purification: Recrystallised from petroleum ether (60-90°C). Approximately 80 ml per gram of crude product was used and the solution was not boiled as this tended to cause the product to seperate out as an oil.

Yield: 72,6%

Melting point: 83,0-85,0°C (Lit[65] m.p. = 84-85,5°C).

Analysis: $C_8H_{12}NO_3P$ M.M. = 201,154 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 47,75% | H = 5,95% | N = 6,90% |
| Calculated: | C = 47,76% | H = 6,01% | N = 6,96% |

NMR ($CDCl_3$): δ3,78 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,66 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,88 - 7,38 (M, 5H, Ph).

#### (b) Dimethyl N-(2 methylphenyl) phosphoramidate

Purification: Recrystallised from petroleum ether (60-80°C) and benzene mixture (3:1).

Yield: 58,9%

Melting point: 110-111,5°C

Analysis: $C_9H_{14}NO_3P$ M.M. = 215,180 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 50,3% | H = 6,6% | N = 6,5% |
| Calculated: | C = 50,23% | H = 6,56% | N = 6,51% |

NMR ($CDCl_3$) δ2,26 (S, 3H, $-CH_3$)

δ3,76 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,02 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,80 - 7,28 (M, 4H, Ph).

(c) Dimethyl N-(3 methylphenyl) phosphoramidate

Purification: Recrystallised from petroleum ether (60-90°C) and benzene mixture (1:3).

Yield: -

Melting point: 81-82°C

Analysis: $C_9H_{14}NO_3P$ M.M. = 215,180 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 50,3% | H = 6,75% | N = 6,55% |
| Calculated: | C = 50,23% | H = 6,56% | N = 6,51% |

NMR ($CDCl_3$): δ2,32 (S, 3H, $-CH_3$)

δ3,78 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,56 - 7,26 (M, 5H, Ph and -NH-).

(d) Dimethyl N-(4 methylphenyl) phosphoramidate

Purification: Recrystallised from petroleum ether (60-90°C) and benzene mixture (3:1).

Yield: -

Melting point: 110-112°C

Analysis: $C_9H_{14}NO_3P$ M.M. = 215,180 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 50,20% | H = 6,65% | N = 6,50% |
| Calculated: | C = 50,23% | H = 6,56% | N = 6,51% |

NMR ($CDCl_3$) δ2,28 (S, 3H, $-CH_3$)

δ3,76 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,63 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,92 (D, 2H, $J_{HH}$ = 8 Hz, Ph)

δ7,06 (D, 2H, $J_{HH}$ = 8 Hz, Ph).

(e) Dimethyl N-(3,4 dimethylphenyl) phosphoramidate

Purification: Recrystallised from petroleum ether (60-90°C) and benzene mixture (4:1).

Yield: -

Melting point: 121-122°C

Analysis: $C_{10}H_{16}NO_3P$ M.M. = 229,206 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 52,35% | H = 7,0% | N = 6,1% |
| Calculated: | C = 52,40% | H = 7,04% | N = 6,11% |

NMR ($CDCl_3$)

δ2,19 (S, 3H, $-CH_3$)

δ2,23 (S, 3H, $-CH_3$)

δ2,77 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,45 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,72 (D, 2H, $J_{HH}$ = 7 Hz, Ph)

δ7,01 (D, 1H, $J_{HH}$ = 8 Hz, Ph).

(f) Dimethyl N-(2,6 dimethylphenyl) phosphoramidate

Purification: The product crystallised from the oil on standing, was filtered and washed with petroleum ether (60-90°C). No further purification was performed.

Yield: 35,7%

Melting point: 122,5-123,5°C

Analysis: $C_{10}H_{16}NO_3P$ M.M. = 229,206 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 52,5% | H = 7,2% | N = 6,2% |
| Calculated: | C = 52,40% | H = 7,04% | N = 6,11% |

NMR ($CDCl_3$)

δ2,39 (S, 6H, $-CH_3$)

δ2,75 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ4,28 (S (Broad), 1H, -NH-)

δ7,02 (S, 3H, Ph).

(g) Dimethyl N-methyl N-phenyl phosphoramidate

Purification: Distillation under reduced pressure afforded a mixture of products which were seperated using a silica gel column and chloroform/acetone (9:1) mixture as eluent. The last band to be eluted was the product but it had to be passed through another two columns before satisfactory purity was obtained.

Yield: 56%

Boiling point: 96°C / 0,01 mm Hg (Lit.[66] b.p. = 92°C/0,25 mm Hg).

Analysis: $C_9H_{14}NO_3P$ M.M. = 215,180 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 52,77% | H = 6,62% | N = 6,85% |
| Calculated: | C = 50,23% | H = 6,56% | N = 6,51% |

NMR ($CDCl_3$): δ3,16 (D, 3H, $J_{HP}$ = 9 Hz, $-NCH_3-$)

δ3,66 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,94-7,40 (M, 5H, Ph)

(h) Dimethyl N-(2 ethylphenyl) phosphoramidate

Purification: The product crystallised from the resulting oil on standing, was filtered and washed with a small quantity of petroleum ether (60-90°C). No further purification was performed.

Yield: 14,6%

Melting point: 79,5-80,5°C.

Analysis: $C_{10}H_{16}NO_3P$ M.M. = 229,206 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 52,45% | H = 7,1% | N = 6,1% |
| Calculated: | C = 52,40% | H = 7,04% | N = 6,11% |

NMR ($CDCl_3$): δ1,24 (T, 3H, $J_{HH}$ = 8 Hz, $-CH_3$)

δ2,59 (Q, 2H, $J_{HH}$ = 8 Hz, $-CH_2-$)

δ3,77 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ4,98 (D, 1H, $J_{HP}$ = 8 Hz, -NH-)

δ6,86 - 7,30 (M, 4H, Ph).

(i) Dimethyl N-(4 ethylphenyl) phosphoramidate

Purification: The product which crystallised from the resulting oil on standing, was filtered, washed with petroleum ether (60-90°C) and recrystallised from petroleum ether (60-90°C).

Yield: 81,5%

Melting point: 95-96,5°C

Analysis: $C_{10}H_{16}NO_3P$ M.M. = 229,206 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 52,3% | H = 6,95% | N = 6,1% |
| Calculated: | C = 52,40% | H = 7,04% | N = 6,11% |

NMR ($CDCl_3$): δ1,20 (T, 3H, $J_{HH}$ = 8 Hz, $-CH_3$)

δ2,59 (Q, 2H, $J_{HH}$ = 8 Hz, $-CH_2-$)

δ3,77 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,62 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,95 (D, 2H, $J_{HH}$ = 8 Hz, Ph)

δ7,10 (D, 2H, $J_{HH}$ = 8 Hz, Ph)

(j) Dimethyl N-(4n butylphenyl) phosphoramidate

Purification: The product crystallised from the resulting oil on standing, was filtered and washed with petroleum ether (60-90°C) then recrystallised from petroleum ether (60-90°C) to which a small quantity of benzene was added to assist dissolution.

Yield: 75,0%

Melting point: 69-71,5°C

Analysis: $C_{12}H_{20}NO_3P$ M.M. = 257,258 gm/mole

Found: C = 55,85% H = 7,9% N = 5,45%

Calculated: C = 56,02% H = 7,84% N = 5,45%

NMR ($CDCl_3$): δ0,91 (T, 3H, $J_{HH}$ = 7 Hz, $-CH_3$)

δ1,14-1,74 (M, 4H, $-CH_2-CH_2-$)

δ2,54 (T, 2H, $J_{HH}$ = 8 Hz, $-CH_2-$)

δ3,77 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,81 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,96 (D, 2H, $J_{HH}$ = 9 Hz, Ph)

δ7,06 (D, 2H, $J_{HH}$ = 9 Hz, Ph).

k) Dimethyl N-(2 tert-butylphenyl) phosphoramidate

Purification: A small quantity of an oily product was obtained. The NMR and TLC show the presence of some unreacted 2-tert-butyl aniline. This contamination did not however interfere with kinetic measurements and the crude product was used for further studies.

Analysis: $C_{12}H_{20}NO_3P$ M.M. = 257,258 gm/mole

Found: C = 58,5% H = 8,1% N = 5,3%

Calculated: C = 56,02% H = 7,85% N = 5,45%

NMR ($CDCl_3$): δ1,30 (S, 9H, $-C(CH_3)_3$)

δ3,76 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,62-7,38 (M, 5H, -NH- and Ph)

l) Dimethyl N-(4-tert-butylphenyl) phosphoramidate

Purification: The crude solid product was recrystallised twice from petroleum ether (60-90°C).

Yield: 77%

Melting point: 103-105°C.

Analysis: $C_{12}H_{20}NO_3P$ M.M. = 257,258 gm/mole

Found: C = 55,10% H = 7,65% N = 5,30%

Calculated: C = 56,01% H = 7,85% N = 5,45%.

NMR ($CDCl_3$): δ1,29 (S, 9H, $-C(CH_3)_3$)

δ3,79 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,77 (S (Broad), 1H, -NH-)

δ6,93 (D, 2H, $J_{HH}$ = 9 Hz, Ph)

δ7,30 (D, 2H, $J_{HH}$ = 9 Hz, Ph).

(m) Dimethyl N-(4-methoxyphenyl) phosphoramidate

Purification: The product crystallised from the resulting oil on standing, was filtered and recrystallised twice from petroleum ether (60-80°C).

Yield: -

Melting point: 68-69°C

Analysis: $C_9H_{14}NO_4P$ M.M. = 231,180 gm/mole

Found: C = 46,45% H = 6,10% N = 5,95%

Calculated: C = 46,76% H = 6,10% N = 6,06%

NMR ($CDCl_3$) δ3,76 (S, 3H, $-OCH_3$)

δ3,76 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,38 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,78 (D, 2H, $J_{HH}$ = 9 Hz, Ph)

δ6,98 (D, 2H, $J_{HH}$ = 9 Hz, Ph).

(n) Dimethyl N-(3 fluorophenyl) phosphoramidate

Purification: The oil obtained was distilled under reduced pressure to yield a solid product which was not purified further.

Yield: -

Melting point: 57-58°C

Analysis: $C_8H_{11}NO_3PF$ M.M. = 219,146 gm/mole

Found: C = 42,05% H = 5,10% N = 5,95%

Calculated: C = 43,84% H = 5,06% N = 6,39%

NMR ($CDCl_3$): δ3,78 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,52-6,88 (M, 3H, Ph)

δ7,14 (T, 1H, $J_{HH}$ = 8 Hz, Ph)

δ7,42 (S (broad), 1H, -NH-)

(o) Dimethyl N-(4 fluorophenyl) phosphoramidate

Purification: The product crystallised from the resulting oil on standing, was filtered and recrystallised from a small volume of benzene.

Yield: -

Melting point: 74-75°C

Analysis: $C_8H_{11}NO_3PF$ M.M. = 219,146 gm/mole

Found: C = 43,90% H = 5,10% N = 6,45%

Calculated: C = 43,84% H = 5,06% N = 6,39%

NMR ($CDCl_3$): δ3,77 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,86 - 7,08 (M, 4H, Ph)

δ7,42 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

(p) Dimethyl N-(4-N'N'-dimethylaminophenyl) phosphoramidate

Purification: The solid crude product was dissolved in a small volume of ethanol, passed through a column (25 cm, Merck silica gel 60, particle size 0,063-0,200 mm) and eluted with ethanol. The first band to be eluted was collected and the solvent removed to leave a dark oil which crystallised on standing. The crystals were recrystallised twice from petroleum ether / benzene (4:1).

Yield: -

Melting point: 95-97°C

Analysis: $C_{10}H_{17}N_2O_3P$ M.M. = 244,224 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 49,05% | H = 6,8% | N = 11,4% |
| Calculated: | C = 49,17% | H = 7,02% | N = 11,47% |

NMR ($CDCl_3$): δ2,88 (S, 6H, $-N(CH_3)_2$)

δ3,76 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,36 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,66 (D, 2H, $J_{HH}$ = 9 Hz, Ph)

δ6,94 (D, 2H, $J_{HH}$ = 9 Hz, Ph).

(q) Dimethyl N-(4 phenoxyphenyl) phosphoramidate

Purification: A dark oil which crystallised on standing was obtained and the crystals were dissolved in a small volume of benzene. Petroleum ether was added and the product precipitated out of solution on cooling. No further purification was carried out.

Yield: -

Melting point: 123-124°C

Analysis: $C_{14}H_{16}NO_4P$ M.M. = 293,246 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 57,3% | H = 5,5% | N = 4,85% |
| Calculated: | C = 57,34% | H = 5,50% | N = 4,78% |

NMR($CDCl_3$): δ3,78 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ6,13 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ6,98 (S, 5H, $-OCH_3$)

δ7,18-7,42 (M, 4H, Ph).

(r) Dimethyl N-(4 biphenyl) phosphoramidate

Purification: Recrystallised from benzene/hexane mixture

Yield: -

Melting point: 144-145°C

Analysis: $C_{14}H_{16}NO_3P$ M.M. = 277,246 gm/mole

Found: C = 60,60% H = 5,85% N = 5,20%

Calculated: C = 60,64% H = 5,82% N = 5,05%

NMR ($CDCl_3$) δ3,82 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,72-5,96 (S (broad), 1H, -NH-)

δ7,06 (D, 2H, $J_{HH}$ = 8 Hz, Ph)

δ7,30 (D, 2H, $J_{HH}$ = 8 Hz, Ph)

δ7,30-7,62 (M, 5H, $-C_6H_5$).

3.6.2 Data on compounds prepared using method 3.5.2

(a) Dimethyl N-(3 methoxyphenyl) phosphoramidate

Purification: The oil obtained was passed through a column (40 cm, Merck silica gel 60, particle size 0,040-0,063 mm) with benzene as eluent and changing to chloroform once the first band had been eluted. The second band was collected and the solvent removed to give an oil which crystallised on standing. The crystals were washed with a small quantity of petroleum ether / carbon tetrachloride (3:1) mixture.

Yield: 20,2%

Melting point: 57-60°C

Analysis: $C_9H_{14}NO_4P$ M.M. = 231,180 gm/mole

Found: C = 46,4% H = 6,3% N = 6,0%

Calculated: C = 46,76% H = 6,10% N = 6,06%

NMR ($CDCl_3$): δ3,79 (S, 3H, $-OCH_3$)

δ3,79 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ5,78 (S (broad), 1H, -NH-)

δ6,44-6,68 (M, 3H, Ph)

δ7,04-7,20 (M, 1H, Ph)

(b) Dimethyl N-(3 nitrophenyl) phosphoramidate

Purification: The solid product was recrystallised from aqueous methanol.

Yield: -

Melting point: 148-150°C.

Analysis: $C_8H_{11}N_2O_5P$ M.M. = 246,155 gm/mole

Found: C = 39,0% H = 4,4% N = 11,5%

Calculated: C = 39,03% H = 4,50% N = 11,38%

NMR ($CDCl_3$) δ3,82 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ7,08 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ7,22-7,54 (M, 2H, Ph)

δ7,74-7,94 (M, 1H, Ph).

(c) Dimethyl N-(4 nitrophenyl) phosphoramidate

Purification: The solid crude product was recrystallised from a benzene / petroleum ether (60-90°C) (4:1) mixture to which a small quantity of chloroform was added to facilitate dissolution.

Yield: -

Melting point: 164-165°C

Analysis: $C_8H_{11}N_2O_5P$ M.M. = 246,155 gm/mole

| | | | |
|---|---|---|---|
| Found: | C = 39,05% | H = 4,45% | N = 11,45% |
| Calculated: | C = 39,03% | H = 4,50% | N = 11,38% |

NMR ($CDCl_3$): δ3,82 (D, 6H, $J_{HP}$ = 11 Hz, $-OCH_3$)

δ7,10 (D, 2H, $J_{HH}$ = 9 Hz, Ph)

δ7,88 (D, 1H, $J_{HP}$ = 10 Hz, -NH-)

δ8,16 (D, 2H, $J_{HH}$ = 9 Hz, Ph).

# CHAPTER FOUR

# SUPPLEMENTARY INFORMATION

# 4 SUPPLEMENTARY INFORMATION

## 4.1 Information on the tables

The abbreviations used in the tables 4.1 - 4.8 have the following meanings and units:

$A_t$ = Absorbance of the substrate at time, t, at the wavelength indicated.

$A_\infty$ = Absorbance of the substrate on completion of the reaction at the same wavelength as $A_t$.

Conc = Initial concentration of substrate used for UV spectrophotometric determinations of acidic hydrolysis rates. (mole/liter).

$\varepsilon_{max}$ = Molecular extinction coefficient at the wavelength indicated for maximum absorbance. (liter $mole^{-1}$ $cm^{-1}$).

$k_\psi$ = Observed rate constant ($sec^{-1}$).

$k_{rel}$ = Relative rate constant.

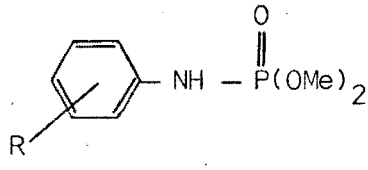
$$= \frac{\text{rate constant of dimethyl N (alkyl substituted phenyl) phosphoramidate}}{\text{rate constant of dimethyl N (phenyl) phosphoramidate}}$$

$\lambda_{max}$ = Wavelength of absorbance maximum at which the reaction was monitored (mμ)

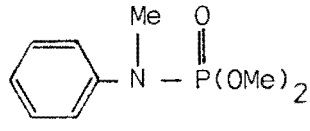
ΔpKa = Difference between pKa values for substituted and unsubstituted anilinium ions

$= (pK_R - pK_H)$

R = Ring substituent as indicated below:




Note: When R = NMe the substrate is:




r = Correlation coefficient indicating the correlation between the experimental values and the "best fit" curve obtained from

the least squares method. The value 1,0000 indicates perfect correlation.

Std Dev = Standard deviation.

T = Absolute temperature ($^{o}K$) except where indicated otherwise.

$t_{\frac{1}{2}}$ mon = The number of half lives for which the reaction was monitored.

Note:

Values in the columns must be multiplied by the factor in brackets at the head of the column.

The tables 4.1 - 4.4 are examples of the results obtained from the experimentally determined graph of decrease in absorbance with time. (The hydrolysis reactions were performed in a solution of 3,47 M sulphuric acid in 20% dioxane/water). The rate constant, $k_{\psi}$, half life, $t_{\frac{1}{2}}$, and molecular extinction coefficient, $\varepsilon$, can then be determined from the plot of $\ln(A_t - A_\infty)$ vs time (Figures 4A - 4D) as explained in chapter 2.

Tables 4.5 - 4.8 list the results obtained from the plots of $\ln(A_t - A_\infty)$ vs time for dimethyl N-(alkyl substituted phenyl) phosphoramidates with substituents indicated by "R".

Table 4.5 Results obtained from 3,51 M $H_2SO_4$ in dioxane/water

Table 4.6 Results obtained from 3,47 M $H_2SO_4$ in dioxane/water

Table 4.7 Results obtained from 3.49 M $H_2SO_4$ in dioxane/water

A. Hydrolysis of dimethyl N-(phenyl) phosphoramidate (Table 4.1)

Conc = $1,0688 \times 10^{-3}$ M

$\lambda_{max}$ = 274 mμ.

Temp = 25,0°C.

Results from figure 4A

$k_{\psi}$ = 1,2274 x $10^{-4}$ $sec^{-1}$

$t_{\frac{1}{2}}$ = 94,1 min.

$\epsilon$ = 879,5 lit $mole^{-1}$ $cm^{-1}$

r = 0,9999

B. Hydrolysis of dimethyl N-(2 methylphenyl) phosphoramidate (Table 4.2)

Conc = 1,3779 x $10^{-3}$ M

$\lambda_{max}$ = 272,5 mμ

Temp = 25,0°C

Results from figure 4B

$k_{\psi}$ = 0,8576 x $10^{-4}$ $sec^{-1}$

$t_{\frac{1}{2}}$ = 134,7 min.

$\epsilon$ = 720,2 lit $mole^{-1}$ $cm^{-1}$

r = 0,9999

C. Hydrolysis of dimethyl N-(4 methylphenyl) phosphoramidate (Table 4.3)

Conc = 1,1228x $10^{-3}$ M

$\lambda_{max}$ = 279,5 mμ

Temp = 25,0°C

Results from figure 4C

$k_{\psi}$ = 1,9386 x $10^{-4}$ $sec^{-1}$

$t_{\frac{1}{2}}$ = 59,6 min.

$\epsilon$ = 1055,5 lit $mole^{-1}$ $cm^{-1}$

r = 0,9999

D. Hydrolysis of dimethyl N-methyl, N-phenyl phosphoramidate (Table 4.4)

Conc = $2,9705 \times 10^{-3}$ M

$\lambda_{max}$ = 270 mμ

Temp = 25,0°C

Results from figure 4D

$k_{\psi}$ = $29,4301 \times 10^{-4}$ $sec^{-1}$

$t_{\frac{1}{2}}$ = 3,9 min.

ε = 283,9 lit $mole^{-1}$ $cm^{-1}$

r = 0,9998

TABLE 4.1 (Results for graph 4A)

| Time (min) | Absorbance ($A_t$) | $\ln(A_t - A_\infty)$ |
|---|---|---|
| 5 | 0,8967 | -0,1147 |
| 10 | 0,8660 | -0,1497 |
| 15 | 0,8340 | -0,1875 |
| 30 | 0,7513 | -0,2926 |
| 45 | 0,6740 | -0,4020 |
| 60 | 0,6067 | -0,5080 |
| 75 | 0,5453 | -0,6156 |
| 90 | 0,4900 | -0,7236 |
| 105 | 0,4407 | -0,8309 |
| 120 | 0,3947 | -0,9425 |
| 135 | 0,3533 | -1,0546 |
| 150 | 0,3167 | -1,1658 |
| 165 | 0,2847 | -1,2742 |
| 180 | 0,2547 | -1,3876 |
| 195 | 0,2273 | -1,5036 |
| 210 | 0,2040 | -1,6144 |
| 225 | 0,1840 | -1,7204 |
| 240 | 0,1647 | -1,8347 |
| 255 | 0,1480 | -1,9449 |
| 270 | 0,1327 | -2,0583 |
| 285 | 0,1200 | -2,1628 |
| 300 | 0,1073 | -2,2795 |
| 315 | 0,0967 | -2,3896 |
| 330 | 0,0867 | -2,5051 |
| 345 | 0,0780 | -2,6173 |
| $t_\infty$ | 0,005 | - |

TABLE 4.2 (Results for graph 4B)

| Time (min) | Absorbance ($A_t$) | $\ln(A_t-A_\infty)$ |
|---|---|---|
| 5 | 0,9693 | -0,0615 |
| 10 | 0,9480 | -0,0845 |
| 30 | 0,8580 | -0,1875 |
| 50 | 0,7767 | -0,2908 |
| 70 | 0,7027 | -0,3950 |
| 90 | 0,6340 | -0,5025 |
| 110 | 0,5773 | -0,6009 |
| 130 | 0,5240 | -0,7032 |
| 150 | 0,4747 | -0,8082 |
| 170 | 0,4293 | -0,9155 |
| 190 | 0,3893 | -1,0207 |
| 210 | 0,3553 | -1,1198 |
| 230 | 0,3240 | -1,2208 |
| 250 | 0,2933 | -1,3305 |
| 270 | 0,2680 | -1,4313 |
| 290 | 0,2447 | -1,5340 |
| 310 | 0,2227 | -1,6416 |
| 330 | 0,2040 | -1,7430 |
| 350 | 0,1880 | -1,8388 |
| 370 | 0,1720 | -1,9449 |
| 390 | 0,1587 | -2,0428 |
| 410 | 0,1467 | -2,1399 |
| 430 | 0,1347 | -2,2475 |
| 450 | 0,1247 | -2,3469 |
| 470 | 0,1147 | -2,4573 |
| 490 | 0,1067 | -2,5553 |
| 510 | 0,0993 | -2,6545 |
| 530 | 0,0920 | -2,7646 |
| $t_\infty$ | 0,029 | - |

TABLE 4.3 (Results for graph 4C)

| Time (min) | Absorbance ($A_t$) | $\ln(A_t - A_\infty)$ |
|---|---|---|
| 5 | 1,1253 | 0,1127 |
| 10 | 1,0627 | 0,0551 |
| 15 | 1,0013 | -0,0047 |
| 20 | 0,9467 | -0,0612 |
| 25 | 0,8947 | -0,1180 |
| 30 | 0,8453 | -0,1751 |
| 40 | 0,7560 | -0,2877 |
| 50 | 0,6707 | -0,4085 |
| 60 | 0,5987 | -0,5231 |
| 70 | 0,5320 | -0,6424 |
| 80 | 0,4720 | -0,7636 |
| 90 | 0,4227 | -0,8755 |
| 105 | 0,3533 | -1,0575 |
| 120 | 0,2987 | -1,2287 |
| 135 | 0,2493 | -1,4133 |
| 150 | 0,2107 | -1,5864 |
| 165 | 0,1773 | -1,7641 |
| 180 | 0,1507 | -1,9333 |
| 195 | 0,1293 | -2,0929 |
| 210 | 0,1093 | -2,2698 |
| 225 | 0,0933 | -2,4380 |
| 240 | 0,0800 | -2,6037 |
| $t_\infty$ | 0,006 | - |

TABLE 4.4 (Results for graph 4D)

| Time (min) | Absorbance ($A_t$) | $\ln(A_t - A_\infty)$ |
|---|---|---|
| 1,2 | 0,7013 | -0,4150 |
| 2 | 0,6133 | -0,5580 |
| 3 | 0,5193 | -0,7374 |
| 4 | 0,4393 | -0,9205 |
| 5 | 0,3760 | -1,0936 |
| 6 | 0,3207 | -1,2742 |
| 7 | 0,2747 | -1,4539 |
| 8 | 0,2353 | -1,6382 |
| 9 | 0,2033 | -1,8181 |
| 10 | 0,1760 | -2,0025 |
| 11 | 0,1547 | -2,1745 |
| 12 | 0,1353 | -2,3609 |
| 13 | 0,1207 | -2,5299 |
| 14 | 0,1080 | -2,7031 |
| 15 | 0,0967 | -2,8884 |
| 16 | 0,0880 | -3,0576 |
| 17 | 0,0800 | -3,2442 |
| 18 | 0,0740 | -3,4112 |
| 19 | 0,0693 | -3,5637 |
| 20 | 0,0647 | -3,7437 |
| 21 | 0,0607 | -3,9288 |
| 22 | 0,0580 | -4,0745 |
| 23 | 0,0553 | -4,2451 |
| $t_\infty$ | 0,041 | - |

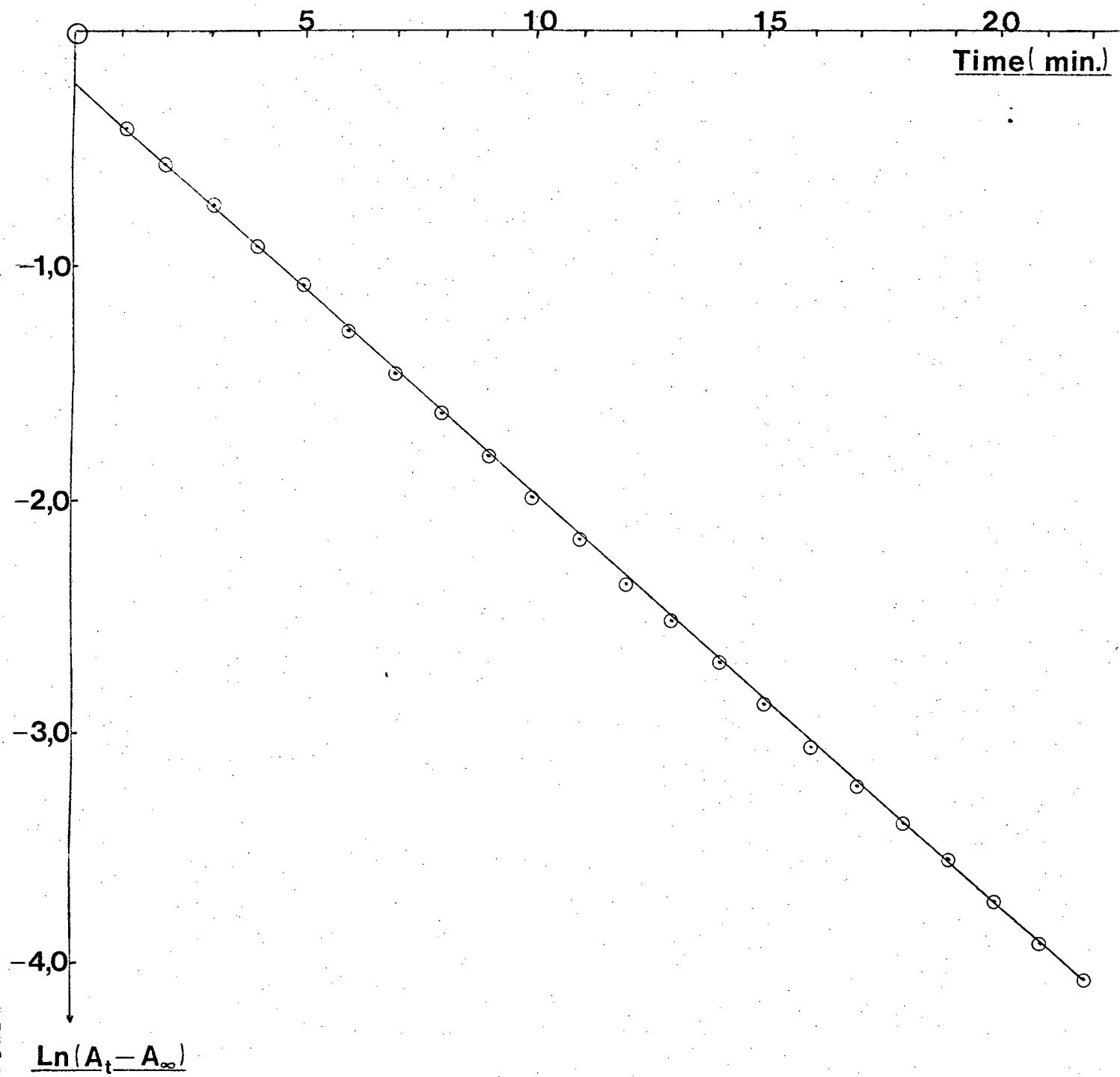



**Fig. 4D**

Decrease in absorbance with time for dimethyl N-methyl, N-phenyl phosphoramidate

TABLE 4.5

| R | Conc.($\times 10^{-3}$) | $t_{\frac{1}{2}}$mon | $k_{\psi}$ ($\times 10^{-4}$) | $\varepsilon_{max}$ | r | $\lambda_{max}$ |
|---|---|---|---|---|---|---|
| H | 1,9125 | 2,69 | 1,1655 | 874,9 | 0,9998 | 273 |
| H | 1,1325 | 2,69 | 1,2040 | 867,4 | 0,9996 | 273 |
| H | 0,7974 | 2,54 | 1,1326 | 858,6 | 0,9998 | 273 |
| H | 1,2478 | 2,94 | 1,0870 | 818,0 | 0,9956 | 273 |
| H | 1,5197 | 3,88 | 1,1585 | 845,0 | 0,9998 | 273 |
| 2 Me | 1,1409 | 2,30 | 0,7968 | 673,6 | 0,9999 | 271 |
| 2 Me | 1,3909 | 2,41 | 0,8151 | 664,7 | 0,9998 | 271 |
| 3 Me | 1,0192 | 3,63 | 1,1150 | 819,4 | 0,9999 | 275 |
| 3 Me | 1,1088 | 3,63 | 1,1971 | 849,9 | 0,9995 | 275 |
| 3 Me | 1,0805 | 3,63 | 1,1836 | 853,1 | 0,9996 | 275 |
| 4 Me | 1,1679 | 5,50 | 1,8302 | 983,1 | 0,9998 | 279 |
| 4 Me | 1,1516 | 5,74 | 1,8517 | 977,8 | 0,9999 | 279 |
| 3,4 diMe | 1,1047 | 4,29 | 1,5548 | 964,9 | 0,9981 | 279 |
| 3,4 diMe | 1,0460 | 4,91 | 1,5932 | 958,3 | 0,9976 | 279 |
| 4 Et | 0,7452 | 5,04 | 1,6178 | 973,1 | 0,9997 | 279 |
| 4 Et | 1,0331 | 5,04 | 1,6169 | 981,6 | 0,9999 | 279 |
| 2 Et | 1,0855 | 1,58 | 0,5051 | 691,0 | 0,9999 | 272 |
| 2 Et | 0,8246 | 2,29 | 0,5112 | 695,5 | 0,9999 | 272 |
| 4*n* Bu | 0,6480 | 4,74 | 1,5052 | 954,0 | 0,9998 | 279 |
| 4*n* Bu | 0,6293 | 4,74 | 1,5365 | 979,1 | 0,9998 | 279 |
| 4*t* Bu | ±0,3879 | 3,88 | 1,2458 | 811,3 | 0,9999 | 278 |

TABLE 4.6

| R | Conc.($\times 10^{-3}$) | $t_{\frac{1}{2}}$ mon | $k_{\psi}$($\times 10^{-4}$) | $\varepsilon_{max}$ | r | $\lambda_{max}$ |
|---|---|---|---|---|---|---|
| H | 1,0688 | 3,67 | 1,2274 | 879,5 | 0,9999 | 274 |
| H | 1,0798 | 3,69 | 1,2359 | 871,3 | 0,9999 | 273,5 |
| 2 Me | 1,3779 | 3,93 | 0,8576 | 720,16 | 0,9999 | 272,5 |
| 2 Me | 1,3626 | 4,09 | 0,8210 | 722,33 | 0,9999 | 272,0 |
| 3 Me | 1,0363 | 4,46 | 1,2729 | 852,12 | 0,9999 | 277 |
| 3 Me | 1,0596 | 3,60 | 1,2226 | 868,7 | 0,9999 | 275 |
| 4 Me | 1,1288 | 4,03 | 1,9386 | 1055,5 | 0,9999 | 279,5 |
| 4 Me | 1,0405 | 3,63 | 1,9486 | 1021,6 | 0,9999 | 280,5 |
| 3,4 diMe | 0,7967 | 4,21 | 1,9448 | 1078,9 | 0,9999 | 280 |
| 3,4 diMe | 0,7256 | 4,34 | 1,8564 | - | 0,9999 | 285,5** |
| 2,6 diMe* | 1,1649 | 3,40 | 0,3117 | - | 0,982 | 206 |
| 2,6 diMe* | 1,1649 | 4,24 | 0,3708 | - | 0,984 | 206 |
| 2 Et | 1,2290 | 3,60 | 0,5430 | 708,03 | 0,9999 | 272 |
| 2 Et | 0,8390 | 3,53 | 0,5233 | 695,4 | 0,9999 | 273 |
| 4 Et | 0,7945 | 3,80 | 1,7569 | 1030,4 | 0,9999 | 279 |
| 4 Et | 0,8333 | 4,12 | 1,7010 | 1017,6 | 0,9999 | 279 |
| 2*t* Bu* | - | 5,10 | 1,3104 | - | 0,9998 | 274,5 |
| 2*t* Bu* | - | 5,08 | 1,3039 | - | 0,9999 | 274,5 |
| 4*t* Bu | 1,0056 | 3,46 | 1,3767 | 906,9 | 0,9999 | 278 |
| 4*t* Bu | 0,9073 | 3,68 | 1,3478 | 879,7 | 0,9999 | 278 |
| N-Me | 2,9705 | 5,85 | 29,4301 | 283,9 | 0,9998 | 270 |
| N-Me | 2,9705 | 5,82 | 29,2388 | 286,16 | 0,9998 | 270 |

* Calculated according to the Guggenheim method.[67]

** This wavelength was used by mistake and is not the wavelength of maximum absorbance.

TABLE 4.7

| R | T | $1/T$ $(\times 10^{-3})$ | Conc. $(\times 10^{-3})$ | $k_\psi$ $(\times 10^{-4})$ | ln $k_\psi$ | $\varepsilon_{max}$ | r | $\lambda_{max}$ |
|---|---|---|---|---|---|---|---|---|
| H | 298,35 | 3,3518 | 1,0316 | 1,1309 | -9,0873 | 875,1 | 0,9999 | 273,5 |
| | 303,35 | 3,2965 | 1,0733 | 1,5818 | -8,7518 | 894,2 | 0,9999 | 273,5 |
| | 308,35 | 3,2431 | 1,0733 | 2,2483 | -8,4002 | 877,0 | 0,9999 | 273,5 |
| | 308,35 | 3,2431 | 1,0733 | 2,2758 | -8,3880 | 889,0 | 0,9999 | 273,5 |
| | 313,55 | 3,1893 | 1,0733 | 3,2854 | -8,0209 | 870,2 | 0,9999 | 273,5 |
| | 313,55 | 3,1893 | 1,0733 | 3,2368 | -8,0358 | 886,5 | 0,9999 | 273,5 |
| | 318,45 | 3,1402 | 1,0733 | 4,7600 | -7,6501 | 856,9 | 0,9999 | 273,5 |
| | 318,45 | 3,1402 | 1,0733 | 4,7940 | -7,6430 | 876,0 | 0,9999 | 273,5 |
| 2 Me | 298,85 | 3,3462 | 1,3393 | 0,7399 | -9,5116 | 741,9 | 0,9997 | 272,5 |
| | 299,05 | 3,3439 | 1,3393 | 0,7666 | -9,4761 | 753,5 | 0,9999 | 272,5 |
| | 303,75 | 3,2922 | 1,3393 | 1,0043 | -9,2060 | 746,8 | 0,9999 | 272,5 |
| | 308,85 | 3,2378 | 1,3393 | 1,3899 | -8,8811 | 742,0 | 0,9999 | 272,5 |
| | 308,85 | 3,2378 | 1,3393 | 1,3789 | -8,8891 | 736,3 | 0,9999 | 272,5 |
| | 313,25 | 3,1923 | 1,3393 | 1,7805 | -8,6335 | 739,3 | 0,9999 | 272,5 |
| | 314,05 | 3,1842 | 1,3393 | 1,7440 | -8,6542 | 720,2 | 0,9999 | 272,5 |
| | 318,75 | 3,1373 | 1,3393 | 2,3525 | -8,3549 | 729,5 | 0,9999 | 272,5 |
| | 318,85 | 3,1363 | 1,3393 | 2,2838 | -8,3845 | 705,4 | 0,9996 | 272,5 |
| 3 Me | 298,35 | 3,3518 | 1,1237 | 1,0955 | -9,1191 | 923,8 | 0,9999 | 276,0 |
| | 298,55 | 3,3495 | 1,1237 | 1,0944 | -9,1201 | 933,3 | 0,9997 | 276,0 |
| | 303,35 | 3,2965 | 1,1237 | 1,5013 | -8,8040 | 902,7 | 0,9999 | 276,0 |
| | 303,45 | 3,2954 | 1,1237 | 1,5108 | -8,7977 | 908,5 | 0,9999 | 276,0 |
| | 308,45 | 3,2420 | 1,1237 | 2,0935 | -8,4715 | 900,9 | 0,9999 | 276,0 |
| | 308,85 | 3,2378 | 1,1237 | 2,3386 | -8,3608 | 944,7 | 0,9988 | 276,0 |
| | 308,85 | 3,2378 | 1,1237 | 2,0279 | -8,5033 | 898,4 | 0,9999 | 276,0 |
| | 313,75 | 3,1873 | 1,1237 | 2,6884 | -8,2214 | 893,1 | 0,9999 | 276,0 |
| | 313,85 | 3,1862 | 1,1237 | 2,9431 | -8,1309 | 896,6 | 0,9999 | 276,0 |
| | 318,45 | 3,1402 | 1,1237 | 4,0739 | -7,8057 | 874,4 | 0,9999 | 276,0 |
| | 318,65 | 3,1382 | 1,1237 | 3,9716 | -7,8312 | 874,4 | 0,9999 | 276,0 |
| 4 Me | 299,65 | 3,3372 | 0,9546 | 1,8039 | -8,6204 | 1090,1 | 0,9999 | 280,0 |
| | 303,35 | 3,2965 | 0,9546 | 2,3866 | -8,3405 | 1061,8 | 0,9999 | 280,0 |
| | 303,45 | 3,2954 | 0,9546 | 2,2779 | -8,3871 | 1055,9 | 0,9999 | 280,0 |

TABLE 4.7 continued/

| R | T | 1/T ($\times 10^{-3}$) | Conc. ($\times 10^{-3}$) | $k_\psi$ ($\times 10^{-4}$) | ln $k_\psi$ | $\varepsilon_{max}$ | r | $\lambda_{max}$ |
|---|---|---|---|---|---|---|---|---|
| 4 Me | 308,15 | 3,2452 | 0,9546 | 3,3530 | -8,0005 | 1075,9 | 0,9998 | 280,0 |
| | 308,65 | 3,2399 | 0,9546 | 3,2769 | -8,0234 | 1076,8 | 0,9998 | 280,0 |
| | 313,65 | 3,1883 | 0,9546 | 4,6739 | -7,6683 | 1053,6 | 0,9999 | 280,0 |
| | 313,65 | 3,1883 | 0,9546 | 4,6354 | -7,6766 | 1064,1 | 0,9999 | 280,0 |
| | 318,75 | 3,1373 | 0,9546 | 6,5410 | -7,3323 | 1050,0 | 0,9956 | 280,0 |
| | 318,85 | 3,1363 | 0,9546 | 6,2395 | -7,3794 | 1041,2 | 0,9999 | 280,0 |
| 2 Et | 298,25 | 3,3529 | 0,9952 | 0,4755 | -9,9537 | 775,9 | 0,9999 | 272,0 |
| | 298,45 | 3,3506 | 0,9952 | 0,4947 | -9,9141 | 757,0 | 0,9999 | 272,0 |
| | 303,35 | 3,2965 | 0,9952 | 0,7228 | -9,5350 | 769,5 | 0,9999 | 272,0 |
| | 303,35 | 3,2965 | 0,9952 | 0,7035 | -9,5620 | 752,8 | 0,9999 | 272,0 |
| | 308,15 | 3,2452 | 0,9952 | 0,9337 | -9,2789 | 738,9 | 0,9999 | 272,0 |
| | 308,15 | 3,2452 | 0,9952 | 0,9493 | -9,2624 | 746,5 | 0,9999 | 272,0 |
| | 313,35 | 3,1913 | 0,9952 | 1,4413 | -8,8448 | 744,5 | 0,9999 | 272,0 |
| | 313,85 | 3,1862 | 0,9952 | 1,3337 | -8,9224 | 745,1 | 0,9999 | 272,0 |
| | 318,95 | 3,1353 | 0,9952 | 2,1923 | -8,4254 | 736,5 | 0,9999 | 272,0 |
| | 319,15 | 3,1333 | 0,9952 | 2,2283 | -8,4091 | 743,3 | 0,9999 | 272,0 |
| 4 Et | 298,45 | 3,3506 | 0,9127 | 1,5192 | -8,7922 | 1080,1 | 0,9999 | 279,5 |
| | 298,55 | 3,3495 | 0,9127 | 1,5023 | -8,8033 | 1066,3 | 0,9999 | 279,5 |
| | 303,15 | 3,2987 | 0,9127 | 2,0395 | -8,4976 | 1069,3 | 0,9999 | 279,5 |
| | 303,45 | 3,2954 | 0,9127 | 2,0162 | -8,5091 | 1074,4 | 0,9999 | 279,5 |
| | 308,35 | 3,2431 | 0,9127 | 2,8277 | -8,1709 | 1084,3 | 0,9999 | 279,5 |
| | 308,75 | 3,2389 | 0,9127 | 2,9035 | -8,1444 | 1064,0 | 0,9999 | 279,5 |
| | 313,35 | 3,1913 | 0,9127 | 3,7107 | -7,8991 | 1076,6 | 0,9999 | 279,5 |
| | 313,75 | 3,1873 | 0,9127 | 3,8657 | -7,8582 | 1064,1 | 0,9998 | 279,5 |
| | 318,75 | 3,1373 | 0,9127 | 5,5332 | -7,4996 | 1047,7 | 0,9999 | 279,5 |
| | 318,75 | 3,1373 | 0,9127 | 5,5583 | -7,4950 | 1088,8 | 0,9999 | 279,5 |
| N Me | 293,15 | 3,4112 | 2,9705 | 21,1643 | -6,1580 | 300,1 | 0,9994 | 270,0 |
| | 293,15 | 3,4112 | 2,9705 | 19,2683 | -6,2519 | 288,0 | 0,9995 | 270,0 |
| | 298,95 | 3,3450 | 2,9705 | 27,8541 | -5,8834 | 287,3 | 0,9999 | 270,0 |
| | 299,55 | 3,3383 | 2,9705 | 29,6120 | -5,8222 | 293,4 | 0,9999 | 270,0 |
| | 303,15 | 3,2987 | 2,9705 | 34,4401 | -5,6711 | 278,3 | 0,9998 | 270,0 |
| | 303,15 | 3,2987 | 2,9705 | 33,5872 | -5,6962 | 275,5 | 0,9992 | 270,0 |

TABLE 4.7 continued/

| R | T | 1/T ($\times 10^{-3}$) | Conc. ($\times 10^{-3}$) | $k_\psi$ ($\times 10^{-4}$) | ln $k_\psi$ | $\varepsilon_{max}$ | r | $\lambda_{max}$ |
|---|---|---|---|---|---|---|---|---|
| N Me | 308,15 | 3,2452 | 2,9705 | 46,1999 | -5,3774 | 246,8 | 0,9998 | 270,0 |
| | 308,15 | 3,2452 | 2,9705 | 44,1719 | -5,4223 | 279,1 | 0,9995 | 270,0 |
| | 313,15 | 3,1934 | 2,9705 | 59,2995 | -5,1277 | 275,4 | 0,9995 | 270,0 |
| | 313,15 | 3,1934 | 2,9705 | 58,0210 | -5,1495 | 272,6 | 0,9997 | 270,0 |

TABLE 4.8

| R | T | Conc. ($\times 10^{-3}$) | $k_{\psi D}$ ($\times 10^{-4}$) | r | $k_{\psi H}$ * ($\times 10^{-4}$) | $\frac{k_{\psi H}}{k_{\psi D}}$ | Mean $k_{\psi H}/k_{\psi D}$ | Std. Dev. |
|---|---|---|---|---|---|---|---|---|
| H | 298,45 | 0,9615 | 2,0176 | 0,9991 | 1,0648 | 0,528 | | |
| | 298,45 | 0,9615 | 2,0277 | 0,9999 | 1,0648 | 0,525 | 0,526 | 0,0019 |
| N Me | 298,15 | 2,8478 | 47,3908 | 0,9960 | 26,3729 | 0,557 | | |
| | 298,35 | 2,8478 | 48,1434 | 0,9972 | 26,3729 | 0,548 | 0,552 | 0,0062 |
| 2 Me | 298,35 | 1,3589 | 1,4942 | 0,9999 | 0,7170 | 0,480 | | |
| | 298,35 | 1,3589 | 1,5139 | 0,9999 | 0,7170 | 0,474 | 0,477 | 0,0042 |

* Values taken from table 4.7

# REFERENCES

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