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Harvard University, Ph.D., 1971
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The Hydrolysis of Some N-Substituted Cyclic Phosphorodiamidates of Ethylenediamine

A thesis presented

by

Lewis David Williams

to

The Department of Chemistry

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

Chemistry

Harvard University

Cambridge, Massachusetts

October, 1970

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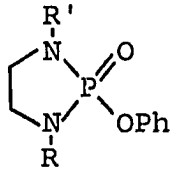
The Hydrolysis of Some N-Substituted Cyclic Phosphorodiamidates of Ethylenediamine

(A Summary)

Research Director
F. H. Westheimer

L. David Williams
September, 1970

The five-membered ring phosphorodiamidates (I) were synthesized, and the rate constants for their hydrolysis in acid and base were determined.



R = H, R'= Me

I R = R'= H,Me,Et,i-Pr,t-Bu,Ph

Many phosphoramidates containing an N-H bond hydrolyze in base much faster than do the corresponding completely substituted (N-Me) compounds. In some cases this rate difference has been shown to be due to the N-H compound's hydrolyzing by a proton-abstraction/elimination path which is not available to the N-Me compound. Knowing the effect of bulky substituents on the rates of hydrolysis should allow one to decide whether for the cyclic compounds this N-H/N-Me rate difference is due to this change in mechanism or to a large steric deceleration of nucleophilic attack.

The rates of hydrolysis of the cyclic amidates in both acid and base were found to be extremely sensitive to the substituent, bulky substituents slowing the rate. The extremes in relative rates were found to be H:Me:t-Bu = $10^{3.4}$:(1):$10^{-7.1}$ in acid, and H:Me:t-Bu = $10^{4.5}$:(1):$10^{<-7.6}$ in base. The results are discussed on the basis of nucleophilic attack on phosphorus showing a large steric and inductive effect.

Somewhat surprisingly, the N-alkyl, but not the N-aryl, cyclic phosphorodiamidates hydrolyze in base predominently with P-N cleavage rather than by loss of PhO^-. This result is not well understood, but is discussed on the basis of a pentacovalent intermediate which must protonate on nitrogen or pseudorotate before breaking down to products.

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Acknowledgements

My special thanks go to Professor Westheimer, whose guidance and example have made the past four years as pleasant and instructive as is reasonably possible; and to my lab-mates, past and present, whose discussions, advice, and presence have provided enormous support.

I am also very grateful to the National Science Foundation for predoctoral fellowships for four years, and to Hampar Janjigian for keeping the NMR spectrometers in better running condition than they wanted to be.

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Abbreviations

DME	1,2-dimethoxyethane
I	ionic strength
M	moles/liter
N	equivalents/liter
PDA	phosphorodiamidate
Cl(Me_2enePDA)	N,N'-dimethylethylenediaminephosphorodiamidochloridate
Ph(H_2enePDA)	phenyl ethylenediaminephosphorodiamidate
Ph(MeHenePDA)	phenyl N-methylethylenediaminephosphordiamidate
Ph(Me_2enePDA)	phenyl N,N'-dimethylethylenediaminephosphorodiamidate
Ph(Et_2enePDA)	phenyl N,N'-diethylethylenediaminephosphorodiamidate
Ph(i-Pr_2enePDA)	phenyl N,N'-di-i-propylethylenediaminephosphorodiamidate
Ph(t-Bu_2enePDA)	phenyl N,N'-di-t-butylethylenediaminephosphorodiamidate
Ph(Ph_2enePDA)	phenyl N,N'-diphenylethylenediaminephosphorodiamidate
Ph(H_2Ph-enePDA)	phenyl o-phenylenediaminephosphorodiamidate
Ph(Ph_2PDA)	phenyl phosphorodianilide
Ph(Me_4PDA)	phenyl tetramethylphosphorodiamidate
p-NO_2-Ph(Ph_2PDA)	p-nitrophenyl phosphorodianilide
Ph(alkyl$_2$enePDA)	phenyl N,N'-dialkylethylenediaminephosphorodiamidate (alkyl = H, Me, Et, etc.)
THF	tetrahydrofuran

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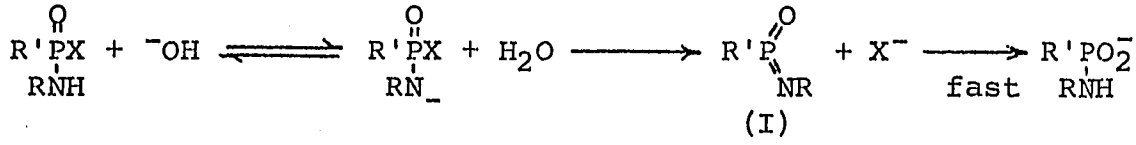
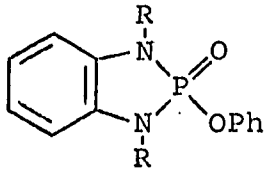
Introduction

The rates of hydrolysis of many phosphoramidates containing an amide hydrogen are several orders of magnitude faster than the rates of hydrolysis of the corresponding phosphoramidates not containing an amide hydrogen [1-5]. There is strong evidence that this rate difference in alkali is due, in at least some cases, to the N-H compounds' hydrolyzing by a proton-abstraction/elimination pathway through a metaphosphoramidate intermediate (I).[2,3,5]



On the basis of the argument that it would be unfavorable to force such a metaphosphoramidate intermediate into a five-member ring, Kerst[4] prepared some o-phenylenediaminephosphorodiamidates (II).



(II), a) R = H
b) R = Me

The expectation was that if the metaphosphoramidate pathway were followed, the rate difference between a) and b) would be small. However, Kerst found that the rates of hydrolysis of the N-H compound in both acid and base were still about 10^4 times faster than the rates of the N-Me compound.[4]

---

1 D. F. Heath, J.Chem.Soc., 3796, 3804(1956)
2 P. S. Traylor, Ph.D. Thesis, Harvard University, 1963
3 P. S. Traylor, F. H. Westheimer, J.Am.Chem.Soc., 87, 553(1965)
4 A. F. Kerst, Ph.D. Thesis, Harvard University, 1967
5 A. F. Gerrard, N. K. Hamer, J.Chem.Soc.(B), 539(1968)

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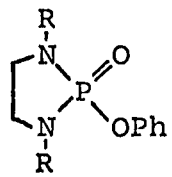
The present work was undertaken as an extension of Kerst's work in an attempt to rationalize the results for the cyclic phosphoramidates. A series of N-substituted ethylenediaminephosphoro-diamidates (III) were prepared and their rates of hydrolysis measured in acid and base.



(III), R = H, Me, Et, i-Pr, t-Bu, Ph

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Historical Background

Even if one ignores the extra complications of buffer catalysis, the hydrolysis of any compound still may show a water rate, acid catalysis, and base catalysis. Each of these pathways will be influenced by what can be called strain, steric, inductive, and resonance effects. Moreover, even seemingly related compounds may actually hydrolyze by different mechanisms. With so many possibilities available, the task of rationalizing the behavior of any small group of compounds must be based on a large volume of previous work. Luckily, the literature of phosphorus chemistry has been reviewed several times [1,2,3].

Water is a relatively poor nucleophile toward phosphorus, so only those compounds containing a good leaving group (such as the P-halides), or containing an ionizable hydrogen that can transfer to give a good leaving group (such as $ROPO_3^-H$), show a detectable water rate.

Acid catalysis seems to fit the same generalization, since it amounts to attack by water on a phosphorus species

---

[1] J. R. Cox, O. B. Ramsey, Chem.Rev., 64, 317(1964)

[2] F. H. Westheimer, Accounts of Chemical Research, 1, 70(1968)

[3] T. C. Bruice, S. J. Benkovic, "Bioorganic Mechanisms," Vol.2 W. A. Benjamin, Inc., New York, 1966, Ch.5

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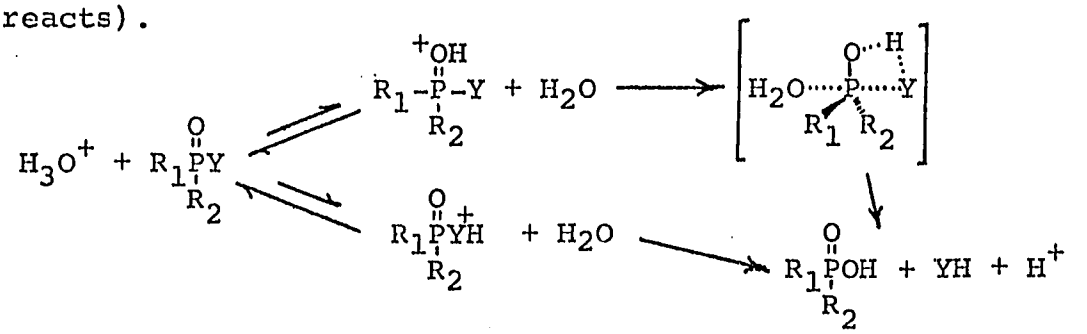
that contains either an ionizable hydrogen (if the $P=\overset{+}{O}-H$ species reacts), or a good leaving group (if the $P-\overset{+}{Y}-H$ species reacts).



Since amine anion is a very poor leaving group, phosphoramides containing no acidic hydrogen show no water rate. This is demonstrated nicely by the results of Öney and Caplow [4]. They compared the rates of hydrolysis of mono- and di-methyl phosphoramidate with that of phosphoramide itself and found that the species without an acidic hydrogen were essentially inert on the time scale involved.

Rates of Hydrolysis of Some Phosphoramidic Esters[4], 37°

	k_{H^+}	$k_{neutral}$	$k_{monoanion}$
$(HO)_2PONH_2$	33.3 $M^{-1}hr^{-1}$	0.42 hr^{-1}	0.25 hr^{-1}
$(MeO)(HO)PONH_2$	5.60	0.58	0
$(MeO)_2PONH_2$	5.55	0	———

Knowledge of the detailed mechanism requires the answers to a number of questions, however. Does proton transfer precede or coincide with the transition state? Does attack by

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[4] I. Öney, M. Caplow, J.Am.Chem.Soc., 89, 6972(1967)

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water come before, during, or after the transition state?

The solvent deuterium isotope effect, $k_{D_3O^+}/k_{H_3O^+} \sim 2$,[5,7] indicates that the acid-catalyzed hydrolysis of phosphoramidates goes by pre-rate-determining-step protonation [6]. Whether attack by water coincides with or follows the transition state is more debatable , and probably varies from case to case.[7,8]

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5 A. W. Garrison, C. E. Boozer, J.Am.Chem.Soc., 90, 3486(1968)

6 W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw Hill, New York, 1969, p 250

7 von G. Tomaschewski, G. Kühn, J.Prakt.Chem., 38, 222(1968)

8 P. Haake, et al., J.Am.Chem.Soc., 92, 3828(1970)

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The base-catalyzed hydrolysis presents a number of interesting problems. As mentioned in the introduction, hydrolysis seems to be able to proceed either by direct nucleophilic attack through a pentacovalent intermediate or transition state, or in certain cases by a proton-abstraction/elimination path. The abstraction/elimination scheme was proposed to explain the rapid alkaline hydrolysis of the phosphoramidic halides containing at least one PNH group[9], and that explanation was strongly supported by Traylor's work on $(Me_2N)_2\overset{O}{\overset{\|}{P}}Cl$ and $(PrNH)_2\overset{O}{\overset{\|}{P}}Cl$ [10]. However, recent work by Gerrard and Hamer has shown that not all fast alkaline hydrolyses of PNH containing compounds proceed through a free metaphosphoramidate intermediate.[11] They studied the hydrolysis of some optically active phosphoramidothioates and found that optical activity was lost during the alkaline hydrolysis of $MeO\overset{S}{\overset{\|}{P}}(NHC_6H_{11})Cl$ [11b], just as expected if the reaction went through a free metaphosphoramidate intermediate, $MeO\overset{S}{\overset{\|}{P}}{=}NC_6H_{11}$. But when the leaving group was p-nitrophenoxide rather than chloride, optical activity was not lost, although the rate for the phosphoramidothioate with an NH bond was 100 times faster than that for the comparable compound without an NH bond.[11c] On the basis of their results, Gerrard and

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9 F. H. Westheimer, Special Publication No. 8, The Chemical Society, London, 1957, p.181

10a) P. S. Traylor, Ph.D. Thesis, Harvard University, 1963

b) P. S. Traylor, F. H. Westheimer, J.Am.Chem.Soc., 87, 553(1965)

11 A. F. Gerrard, N. K. Hamer, J.Chem.Soc.(B) a) 369(1969)
b) 539(1968)
c) 1122(1967)

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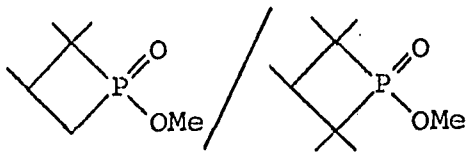
Hamer argue that a free metaphosphoramidate is unlikely to be an intermediate except when the leaving group is very good and the other substituents around phosphorus are not very electronegative[11a].

The alternative explanation, originally proposed by Heath[12], for the rapid hydrolyses of the PNH containing compounds. is that a large steric effect slows the hydrolyses of the completely N-substituted amidates. Such an explanation is clearly inadequate for many of the halides, since attack by water and nucleophiles other than hydroxide do not show this proposed large steric effect.[10] But the steric argument should probably not have been dropped completely, since many cases of large steric effects in the hydrolysis of phosphorus compounds are known[13,14]. Of special significance for the present work is Hawes and Trippett's[15] listing of some relative reactivities in base-catalyzed hydrolysis.



relative k_{OH^-} = 2.6 x10^3

$R_2\overset{O}{\overset{\|}{P}}$-OEt	relative $k_{OH^-}^{120^\circ}$	R= t-Bu	i-Pr	Et
		(1)	500	10^5

12 D. F. Heath, J.Chem.Soc., 3796, 3804(1956)

13 N. J. Death, S. Trippett, Chem.Commun., 172(1969)

14 A. A. Neimyscheva, I. L. Knunyants, J.Gen.Chem.,USSR, 36, 1105(1966)

15 W. Hawes, S. Trippett, Chem.Commun.,577(1968)

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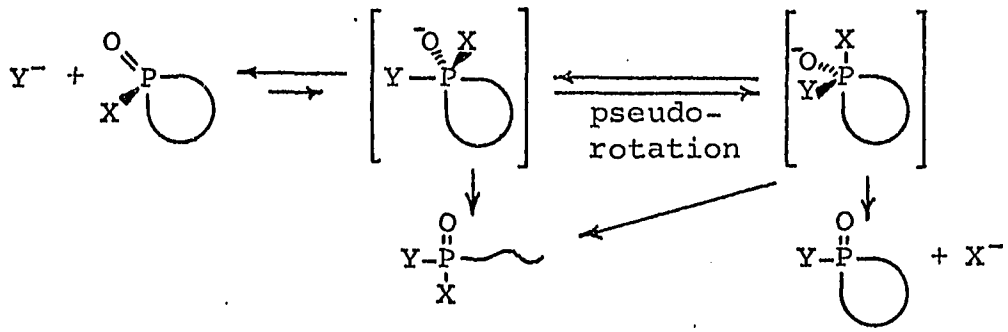
There are two other effects of importance in relation to cyclic phosphorus compounds: ring strain and pseudorotation. Small-ring phosphorus compounds when compared with their acyclic analogues generally show an enhanced rate of reaction with nucleophiles, presumably because of relief of angle-strain in going to a pentacovalent intermediate.



It seems that groups may enter and leave the intermediate only at the axial positions, so for exocyclic cleavage to occur, pseudorotation must take place. This whole topic has been discussed in more detail elsewhere[2].

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Experimental and Results

General Methods

Spectra:

IR	Perkin Elmer Infracord model 137
UV	Cary 15
NMR	Varian A-60 or T-60
mass	Associated Electrical Industries MS-9 with direct insert probe

Melting points (uncorrected):
Thomas-Hoover 6406-H capillary mp apparatus
Fisher-Johns 12-144 hot stage mp apparatus

pH readings:
Radiometer TTT1b Titrator with scale expander
standardized against Fisher Certified pH 4,7,or 10 buffers

Analyses:
Galbraith Analytical Laboratories, Knoxville, Tennesee

Evaporations were carried out under reduced pressure on a Büchi flash evaporator.

Commercial Compounds

All solvents and common inorganic compounds were either Fisher certified, Merck reagent, or Mallinckrodt reagent.

The 1,2-dibromoethane was from Eastman Organic Chemicals.

Anhydrous ethylenediamine was prepared by F. Kerst by distillation of Eastman 98% ethylenediamine from CaH_2.

N-Methylethylenediamine, N,N'-dimethylethylenediamine, N,N'-diethylethylenediamine, and phenyl dichlorophosphate were from Aldrich Chemical Company.

Phenyl phosphate was prepared by reaction of phenyl dichlorophosphate with water.

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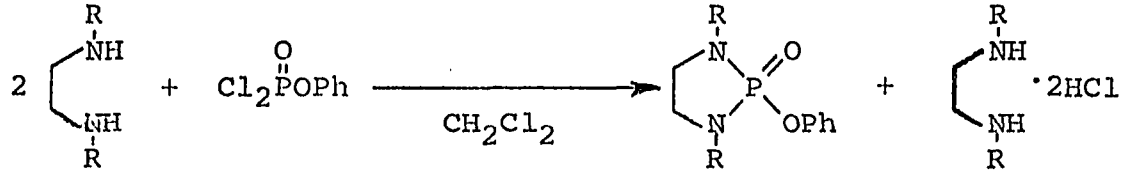
Synthesis of Diamidates

In general, two equivalents of diamine were added to one equivalent of phenyl dichlorophosphate in an inert solvent such as dichloromethane or benzene.



The diamine dihydrochloride was removed by filtration and the PDA purified by distillation or sublimation. Purification was easier when all traces of hydrochloride and other salts were removed by treatment with aqueous base, although this step was impossible for the more reactive amides (e.g. when R = H).

Spectra and elemental analyses are given in Appendix II. They are referenced when available by the abbreviations UV, IR, NMR, mass, analysis.

Products

Knowledge of the products of hydrolysis is based mainly on NMR and UV spectra. In most cases the spectra of the various likely products are different enough from those of starting material and each other that this evidence should suffice, especially given the confirmatory evidence from the other compounds.

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The UV spectra of all the Ph(alkyl$_2$enePDA)'s show a triplet of peaks centered near 260 nm. On hydrolysis the compounds all show similar spectral changes. In acid, the spectrum grows more intense and less sharp. In base, the same changes occur simultaneously with the growth of absorption due to phenoxide ion (Figure 7). Subtracting the absorbance due to PhO^- leaves a spectrum the same as that of the product of acid-catalyzed hydrolysis (see Figure 1 and the discussion under Ph(Me$_2$enePDA) hydrolysis products). Phenyl phosphate gives a spectrum in acid and at neutral pH's similar to that of the ring-opened product, but in base the spectra are quite different (Figure 2). Phenol itself has a much more intense absorption than any of the other products, especially in base (Figure 2).

The NMR spectra complement and help confirm the UV spectral evidence. The P-N-C-H coupling constant of 10-15 cps often allows one to decide what bonds to phosphorus have been broken. This is simplest for the change: doublet due to PNMe changing to singlet due to HNMe.

Supporting the direct spectral evidence are the spectral changes due to secondary reactions. These changes are what one would expect from the chemical transformations: production of phenyl phosphate and free diamine in acid, and neighboring-group-assisted loss of phenoxide ion in base.

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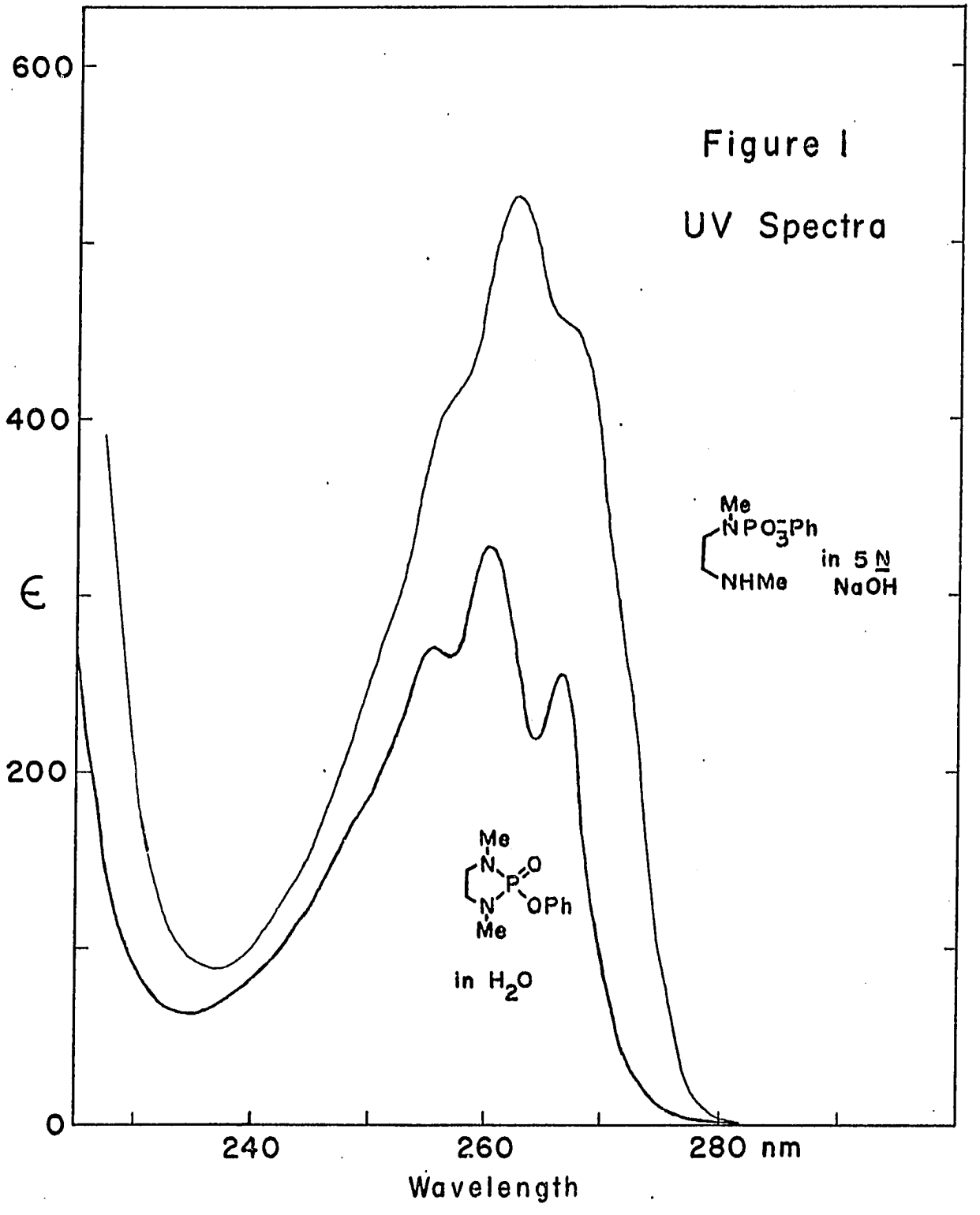

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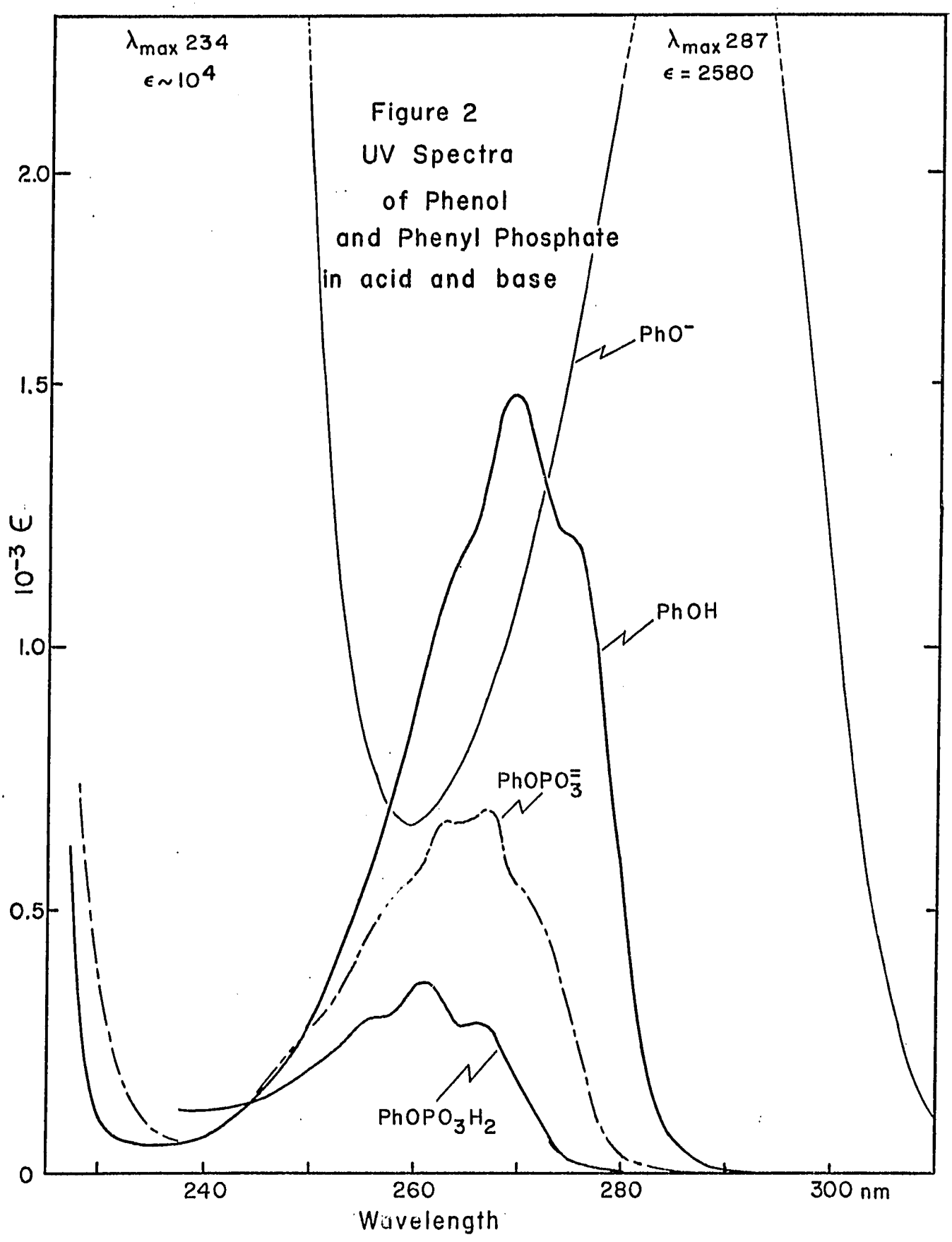

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Kinetic Methods

I. Buffers

Some buffers were prepared according to Long's Biochemists's Handbook[1], others were prepared as integral ratios (e.g.3:1, 1:1, 1:3) of acid to conjugate base. The pH's were measured with the pH meter and glass electrode. The measured pH often changed more than expected[2] on dilution or on changing temperature, but by no more than 0.1 pH unit. This discrepancy was probably due to insufficient equilibration time of the glass electrode in the buffer.

The measured pH's in D_2O or in mixed solvents were corrected to "true" pH's in the normal manner. In D_2O[3]

$$pD = pH_{measured} + (145-t)/(273+t) \qquad t = \text{temperature, } ^\circ C$$

In mixed solvents, a correction term was determined by measuring the pH's of solutions of known acid concentration. For example, in 33% THF at 23°

3.0ml 0.01N HCl + 3.0ml 0.5N KCl + 3.0ml H_2O pH = 2.53
3.0ml 0.01N HCl + 3.0ml 0.5N KCl + 3.0ml THF pH = 2.66

Therefore, $pH_{corr} = pH_{measured} - 0.13$ in 33% THF, I = 0.17N, 23°.

---

1 C. S. Long, editor, "Biochemists' Handbook," Van Norstrand, Princeton, New Jersey, 1961

2 H. S. Harned, B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Co., New York, N. Y., 1958

3 T. H. Fife, T. C. Bruice, J.Phys.Chem., 65, 1079(1961)

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In comparing the rates in solutions of known pH with those in solutions of known hydroxide concentration, account should be taken of the activity coefficient of hydroxide ion. According to Harned and Hamer[4] the value of the ionic activity coefficient product of water, $\gamma_{H^+} \cdot \gamma_{OH^-}/a_{H_2O}$, in 0.2 N KCl at 20-30° (which approximates most of the buffers) is about 0.58. This amounts to a 30% correction in calculating hydroxide concentration from measured pH or in calculating an equivalent pH from a known hydroxide concentration.

$$-\log(\gamma_{OH^-} \cdot c_{OH^-}) = pK_w - pH$$

$$\gamma_{OH^-} \simeq \gamma_{\pm} = \sqrt{\gamma_{H^+} \cdot \gamma_{OH^-}} = \sqrt{0.58} = 0.76 \quad \text{in 0.2 N KCl}$$

$$-\log c_{OH^-} = pK_w - pH - 0.12$$

II. Measurements

For reasonably fast reactions the spectrophotometer cell compartment was thermostatted at the desired temperature, the UV cell containing the buffer solution allowed to equilibrate in the cell compartment for fifteen minutes or more, the compound added either neat (if it was readily soluble in water) or in an inert solvent, the solution mixed with a plunger or by rapidly inverting the stoppered cell several times, and the change in optical density followed as a function of time.

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4 H. S. Harned, W. S. Hamer, J.Am.Chem.Soc., 55, 2204(1933)

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The half-time for thermal equilibration of the UV cell in the thermostatted cell compartment was measured as 2.5 minutes, so 15 minutes equilibration will bring the solution temperature to within 0.1° of the final value if it starts within 6.4° of that value.

Slow reactions were followed by taking spectra of samples drawn from a large volume of solution thermostatted outside the spectrophotometer. In most cases the solution was sealed in Kerst tubes [5], teflon-lined brass tubes with an outlet tube for withdrawing samples. When the internal pressure dropped too low to force more liquid out of the Kerst tube, the pressure was raised by blowing nitrogen in through the outlet tube.

Some hydrolyses were monitored by methods other than UV spectrometry. The course of reaction could sometimes be followed by NMR spectral changes, where the relative concentrations of reactants and products were determined by integration or less accurately by peak heights. In cases where reaction produces acid or base the rate could be measured in the pH-stat: base or acid is automatically added to maintain a constant pH, and this added volume recorded as a function of time.

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[5] A. F. Kerst, Ph.D. Thesis, Harvard University, 1967

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Buffer catalysis was looked for by varying the buffer concentration at constant ionic strength. Catalysis was assumed to be first order in the catalytic species or its kinetic equivalent, the identity of which was then determined from the variation of catalysis rate with pH.

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III. Calculations

The rates of hydrolysis of most of the amides were determined at fixed pH under pseudo first order conditions by recording the change in OD at some wavelength in the UV and plotting the data in the appropriate form to give a straight line.

$A \xrightarrow{k_1} C$ $\qquad C = A_o\ (1-2^{-t/t_{1/2}})$ $\qquad t$ = time, $t_{1/2}$ = half-time $= 0.693/k_1$

a) infinity value known

$$-\log(X_\infty - X_t) = 0.301\ t/t_{1/2} + \text{constant}$$

b) infinity value guessed to give best straight line

$$-\log(X'_\infty - X_t) = 0.301\ t/t_{1/2} + \text{constant}$$

c) Guggenheim plot

$$-\log(X_{t+a} - X_t) = 0.301\ t/t_{1/2} + \text{constant}$$

a = constant time interval

X = any property proportional to % reaction (eg. OD)

In some cases secondary reactions caused a definite drift in the measured OD of the completely hydrolyzed solution. Taking account of the fact that the rate of secondary reaction depends on the concentration of product from the first reaction, and considering only negligible conversion to secondary reaction product,

$$dOD_\infty/dt \ \alpha\ (\text{product})\ \alpha\ (1-2^{-t/t_{1/2}})$$

that is, $dOD_\infty/dt = \beta(1-2^{-t/t_{1/2}})$ where $\beta = dOD_\infty/dt)_{t>5t_{1/2}}$

and integrating,

$$OD_\infty = OD^o_\infty + \beta t + (\beta t_{1/2}/\ln 2)\,2^{-t/t_{1/2}}$$

For calculating $t_{1/2}$ of the first reaction, a linear extrapolation, $OD^t_\infty = OD^o_\infty + \beta t$, is sufficient; but for calculating such things as % exocyclic cleavage, the exact equation must be used to determine the correct OD_∞ at time zero.

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A few reactions followed by NMR spectrometry could not be regarded as pseudo first order because of the high initial concentration of substrate. The rate constant could be determined by plotting the data as a second-order reaction.

$$A + B \xrightarrow{k_2} C \quad , \qquad C_o = 0 \quad , \quad A_o \neq B_o$$

$$k_2 (B_o - A_o) \cdot t = \ln \frac{(1 - C/B_o)}{(1 - C/A_o)}$$

Since the rate constants were determined at a variety of temperatures, some knowledge of the activation parameters is necessary in order to compare the rates for different compounds. The enthalpy of activation for each reaction was determined from a plot of $\log(k/T)$ vs. $1/T$, the slope of which should be $-\Delta H^{\ddagger}/(2.3\ R)$. In most cases the rate constants were too inaccurate and the temperature interval too small for the activation parameters to be at all accurate. These plots are given anyway simply to show all the rate constants in condensed form.

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Phenyl ethylenediaminephosphorodiamidate, Ph(H_2enePDA)

Although the preparation of this cyclic diamidate was reported by Autenrieth and Bölli [1] in 1925, their structure assignment was incorrect. Edmundson [2] repeated the synthesis and obtained a product of similar melting point whose analysis and IR spectrum led him to the conclusion that the hydrolyzed internal salt, rather than the cyclic diamidate, had been obtained. The hydrolytic lability of the cyclic diamidate, as shown in this work and that of F. Kerst [3], explains why neither Autenreith and Bölli nor Edmundson obtained the cyclic product, since both groups ran their syntheses in the presence of water.

The diamidate is easily prepared in the absence of water. A solution of anhydrous ethylenediamine (2.6 g, 40 mmole) in dichloromethane (170 ml) was placed in a serum capped 250 ml flask containing a magnetic stirring bar and cooled to -20° in the freezer. Phenyl dichlorophosphate (4.2 g, 20 mmole) was added by syringe over a period of 3-5 minutes while stirring rapidly. A fine white precipitate formed immediately. After standing overnight, the solution was heated briefly to reflux, then cooled and filtered through a fritted glass disk under a

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1 W. Autenreith, E. Bölli, Ber., 58, 2144(1925)

2 R. S. Edmundson, J.Chem.Soc.(C), 2730(1969)

3 A. F. Kerst, Ph.D. Thesis, Harvard University, 1967

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positive pressure of nitrogen. The first rush of filtrate came through milky, but refiltering after the filter had become partly clogged gave a clear solution. Removal of solvent under vacuum gave a viscous foam which sublimed on heating at 50-100° 10^{-5}mm. The compound sublimed as a clear viscous oil which crystalized only on scratching. The yield was about 0.4 g (10% theory) of white solid, melting at 92.5-94.0° in a capillary. When the melting point was taken between glass cover slips it was considerably lower, 79.0-80.5°, and even in a capillary the compound softened at about 80° where it was in contact with the glass walls.

Ph(H_2enePDA) is soluble in chloroform, dichloromethane, water, methanol, and similar polar solvents; insoluble in carbon tetrachloride, ether, and hydrocarbon solvents.

IR 1 UV analysis (see p 10 and Appendix II)
NMR 1 mass

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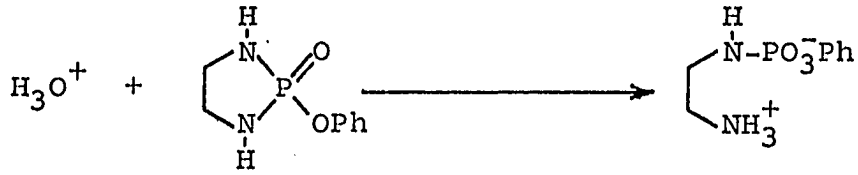
Ph(H_2enePDA) Hydrolysis Products

The product of hydrolysis in acid solution (pH < 9) is the ring-cleaved internal salt.



This assignment is based on both spectral and chemical evidence.

Addition of equivalent amounts of water to the dichloromethane solution of crude Ph(H_2enePDA) gave a white precipitate whose NMR and UV spectra were the same as those of the aqueous hydrolysis product. This solid was used in further work on the hydrolysis product.

Titration of 12.5 mg hydrolysis product in 4.5 ml water with 0.1 N NaOH from an Aminco Automatic Burette, reading the pH with a Radiometer pH meter, showed the presence of one ionizable group in the range pH 6.8-11 (Figure 3). The pK of 9.9±0.1 and the equivalent weight of 200-250 g/mole (216 g/mole expected) is at least consistent with the proposed structure. A more accurate pK and equivalent weight could not be determined because of the dilute solution involved.

A bicarbonate solution of Ph(H_2enePDA) in D_2O produces the acid-catalyzed hydrolysis product. The NMR spectrum of this solution consists of two complex multiplets at δ 3.0 and δ 7.2 (in the ratio of 4.16:5.0), indicating that hydrolysis does not proceed predominantly with cleavage of either the P-OPh or both P-N bonds.

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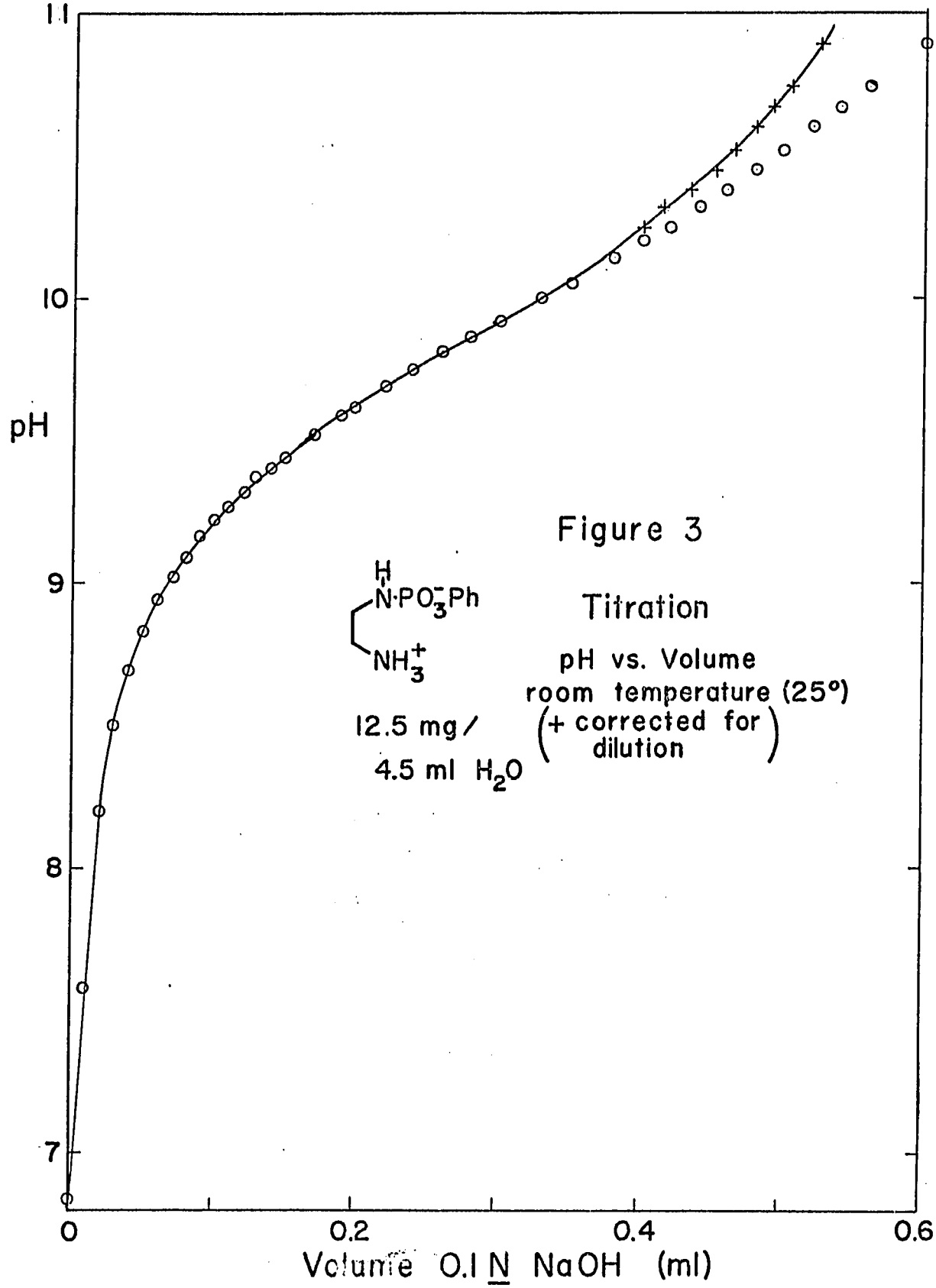

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Comparison of the IR spectrum of the product with that of the ethylenediamine salt of phenyl phosphate (prepared by mixing equivalent amounts of ethylenediamine and phenylphosphoric acid) further demonstrates the nonidentity of these two compounds (IR 2,3).

The analytical data from this and previous work (Table 1) does little except demonstrate the difficulty of purifying these internal phosphate salts.

Table 1

Analytical Data for $^{+}H_3NCH_2CH_2NHPO_3^{-}Ph$

mp	(cryst. solvent)	C	H	N	P	ref.
196°	(ppt from H_2O)			14.47	15.37	a)
195-196	(dioxane-H_2O)	43.6	6.2	12.5	14.15	b)
219-221	(acetone-H_2O)	41.8	6.5	12.1	13.2	b)
200.5-201	(sublimed)			13.1	14.3	b)
196-198	(MeOH-Et_2O)	43.38	5.95			c)
	$C_8H_{11}N_2O_2P$	48.48	5.60	14.13	15.63	calc.
	$C_8H_{13}N_2O_3P$	44.45	6.06	12.96	14.33	calc.

a) Autenreith and Bölli, ref. 1
b) Edmundson, ref. 2
c) this work

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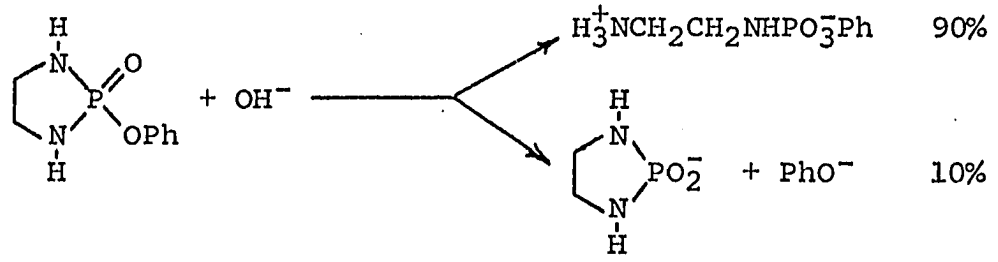
In aqueous base, Ph(H_2enePDA) reacts to give about 10% phenoxide and 90% ring-cleaved amidate.



The evidence for this is the UV spectral behavior. Phenoxide absorption at 233 and 287 nm, and ring-opened amidate absorption at 262 nm, both grow as the hydrolysis proceeds. The % of exocyclic cleavage was calculated from the spectra of solutions used for kinetic measurements and the molar absorbances of the compounds produced.

	ϵ^{262}	ϵ^{287}	ϵ^{310nm}
PhOH	1040	30	0
PhO^-	700	2.58×10^3	100
$RNHPO_3^-Ph$	427	0	0

$$pK_{PhOH} = 9.89$$

therefore,

$$(PhO^-) = \frac{OD^{287} - OD^{310}}{2.48 \times 10^3} \qquad (PhOH) = (PhO^-)10^{9.89-pH}$$

$$OD^{262}_{PhO-} = OD^{287} - (PhO^-)(2.58 \times 10^3 - 700)$$

$$OD^{262}_{PhOH} = (PhOH) \times 1040$$

$$(RNHPO_3^-Ph) = (OD^{262} - OD^{262}_{PhOH} - OD^{262}_{PhO-}) / 427$$

$$\% = \frac{(PhO^-) + (PhOH)}{(PhO^-) + (PhOH) + (RNHPO_3^-Ph)} \times 100$$

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Table 2.
% exocyclic cleavage in the hydrolysis of Ph(H_2enePDA)

pH	$OD^{287}-OD^{310}$	$OD^{262}-OD^{310}$	%	temp.
9.27	0.026	0.550	4.5	30°
"	0.037	0.597	6.0	"
9.74	0.120	0.647	8.8	"
"	0.115	0.618	8.8	"
9.75	0.164	0.890	8.5	"
10.0	0.20	0.83	8.4	"
10.12	0.22	0.74	9.5	"
10.48	0.40	1.05	9.7	"
12.2	0.27	0.57	9.6	"
12.2	0.27	0.64	8.4	20°
13	0.31	0.58	11	"
14	0.222	0.342	14	?

The low percentage of exocyclic cleavage at pH 9.27 is due to the fact that at that pH only half the product is formed by the base catalyzed path (Figure 4), and the acid catalyzed path produces no phenol.

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Ph(H_2enePDA) Hydrolysis Rates

pH	Buffer Solution	I (M)	$t_{1/2}$ (sec)	k_2 ($M^{-1}sec^{-1}$)	temp. (°C)	
				acid		
6.38	phosphate	0.2	7.3	2.29×10^5	19.7	
6.44	phosphate	0.2	5.2	3.69×10^5	29.8	
			5.6	3.30×10^5	"	
6.98	Fisher pH 7 phosphate		24	2.75×10^5	30	
7.03	phosphate	0.2	28.3	2.63×10^5	20.0	
			26.7	2.75×10^5	"	
7.07	phosphate	0.2	23.2	3.47×10^5	29.8	
7.66	phosphate	0.2	122	2.57×10^5	20.0	
7.68	phosphate	0.2	103	3.57×10^5	29.8	
			93	3.22×10^5	"	
8.00	$NaClO_4$	0.5	(310)	2.24×10^5	30.0	a), (tris)
8.80	KCl	0.2	(1310)	3.31×10^5	30.2	a), (NH_3)
9.27	KCl	0.2	(2200)		30.3	a), (NH_3)
9.74	KCl	0.2	(1240)		30.2	a), (NH_3)
9.90	Fisher pH 10 $CO_3^=$, borate		713		30	
				base		
10.12	carbonate	0.2	610	4.37	30.0	b)
10.48	carbonate	0.2	270	4.37	30.0	b)
10.63	carbonate	0.2	710	1.18	20.0	b)
10.60	KCl	0.2	(195)	4.57	30.0	a), (piperidine), b)

a) extrapolated to zero buffer concentration

b) corrected for γ_{OH^-}

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pH	Buffer Solution	I (M)	$t_{1/2}$ (sec)	k_2 ($M^{-1}sec^{-1}$)	temp. (°C)	
				base		
11.06	KCl	0.2	(74)	4.17	30.0	a),(piperidine), b)
11.51	KCl	0.2	(28)	3.90	30.0	a),", b)
	0.01 N NaOH		16	4.33	29.8	
			17	4.07	29.8	
			17.3	4.00	30.0	
	0.02 N NaOH		7.9	4.37	30	
			14.3	2.40	19.7	
	0.1 N NaOH		4.7	1.48	19.6	
pD	D_2O					
				acid		
7.24	phosphate	0.2	16.3	7.40×10^5	30.0	
			15.7	7.68×10^5	"	
				base		
	0.01 N NaOD		12.6	5.50	30.0	
			22.1	3.13	20.0	
	0.0256 N NaOD		5.0	5.40	29.8	
			4.8	5.64	"	
pH_{corr}	33% THF					
5.83	acetate	0.17	8.5	5.5×10^4	25.0	
			7-8.4	$5.6\text{-}6.7 \times 10^4$	"	
5.87	acetate	0.17	10.5-12	$4.3\text{-}4.9 \times 10^4$	"	

In general, the rate constants are accurate to within 10%.

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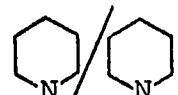
Ph(H_2enePDA) Buffer Catalysis

piperidine

		$t_{1/2}$ (sec)	k_1 (sec^{-1})
1 : 3	0.2 N	130	5.33×10^{-3}
pH 10.60	0.12	150	4.62×10^{-3}
	0.04	177	3.91×10^{-3}
1 : 1	0.2	51	1.36×10^{-2}
pH 11.06		48	1.44×10^{-2}
	0.12	55	1.26×10^{-2}
	0.04	69	1.00×10^{-2}
		66	1.05×10^{-2}
3 : 1	0.2	23	3.01×10^{-2}
pH 11.51	0.12	21	3.30×10^{-2}
	0.04	27	2.56×10^{-2}

ammonia

NH_3/NH_4^+-Cl	NH_4^+-Cl	$t_{1/2}$ (sec)	$k_1 \times 10^4$ (sec^{-1})
1 : 3	0.2 N	1040	6.66
pH 8.80	0.02	1280	5.41
1 : 1	0.2	1400	4.95
pH 9.27	0.02	2100	3.30
3 : 1	0.2	740	9.37
pH 9.74	0.08	960	7.21
	0.02	1160	5.97

Ionic strength held constant at 0.2 N with KCl.
Temperature held at 30.0°.

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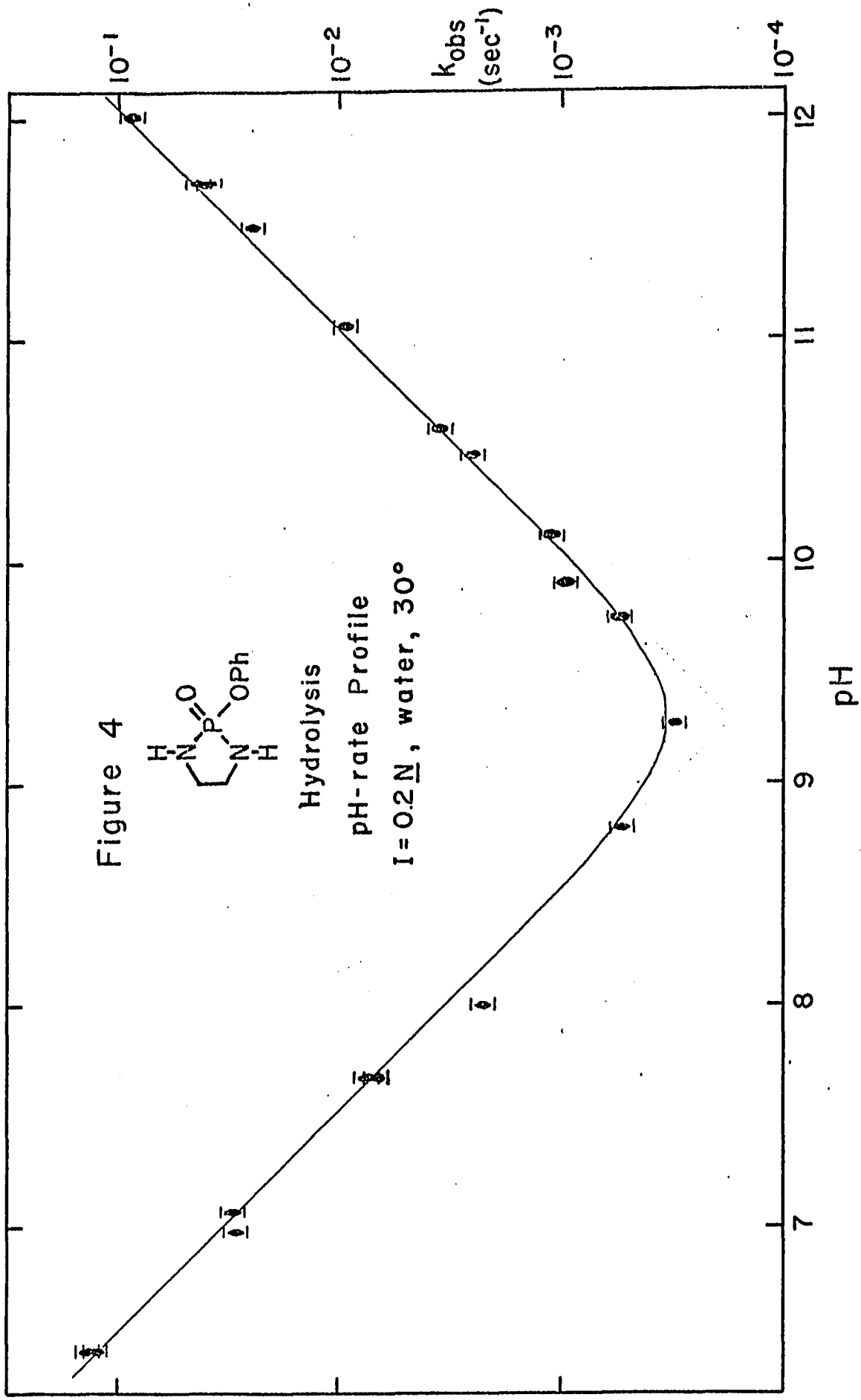

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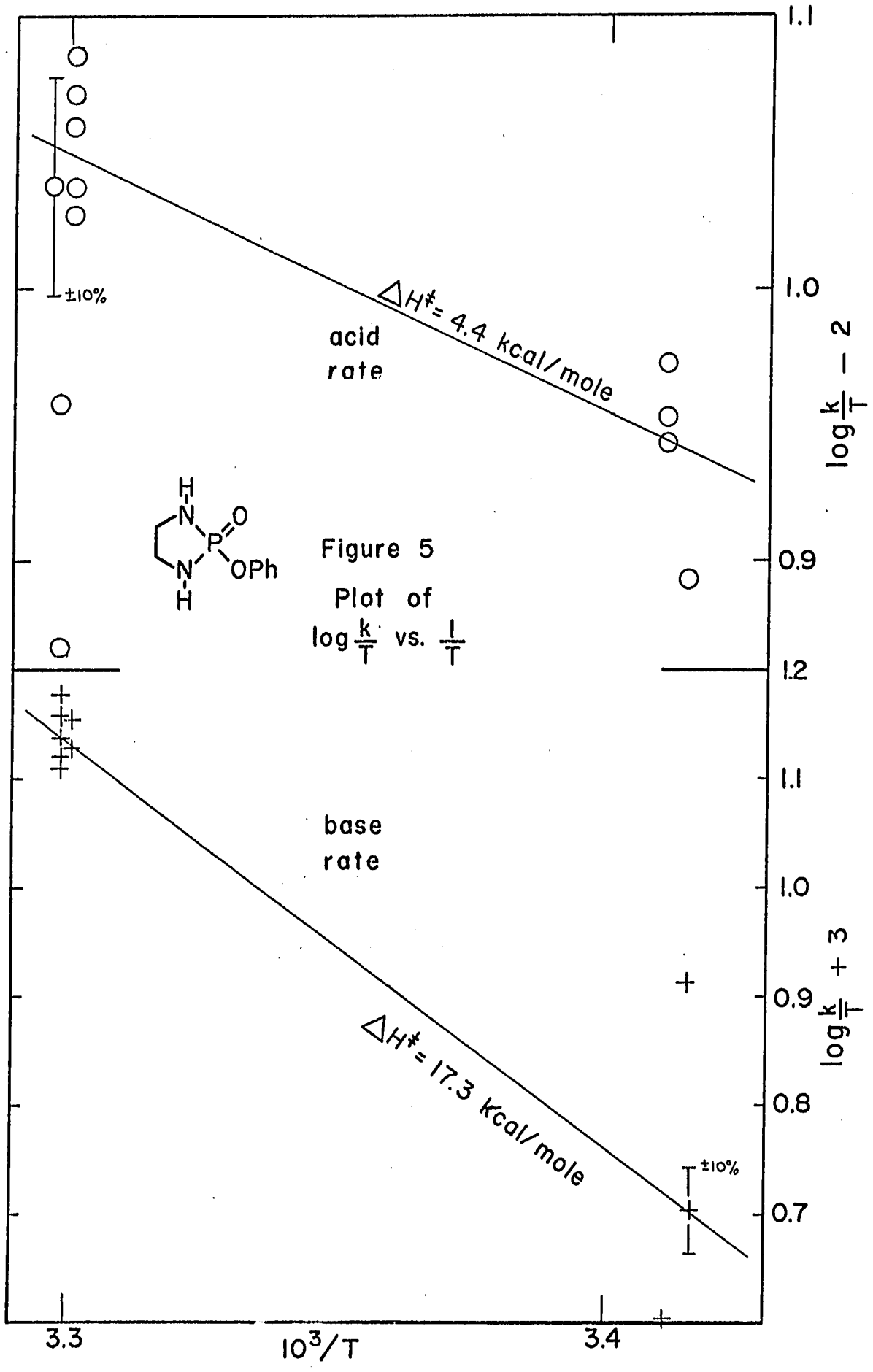

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Ph(H_2enePDA) Secondary Reactions

The cleavage of the second P-N bond in acid was investigated only briefly. A 3.4×10^{-3} N solution of hydrolysis product in 1 N HCl showed no UV spectral changes within a half hour. However, the changes in OD are more favorable in base, so that by withdrawing samples every few minutes and quenching them with alkali to obtain the phosphate anions, the appearance of phenyl phosphate dianion absorption could be observed. This secondary reaction in acid seemed to have a half-time on the order of 10 minutes at room temperature.

The ring-opened amidate reacts in base also, but with production of PhO^- and $H_2NCH_2CH_2NHPO_3^{=}$. The reaction was followed by UV and NMR spectrometry. A solution of 18 mg (0.083 mmole) hydrolysis product, 0.15 g 10 N NaOD (0.9 mmole), and 0.25 g D_2O in an NMR tube was heated at 80° for several days. At intervals the tube was cooled and the NMR spectrum recorded. The formation of PhO^- was followed by the appearance of peaks at δ6.6 (which integrate for 3 of the 5 phenoxide protons) and was essentially quantitative. This reaction had a half-time of 1.1 hours ($k_1 = 1.8 \times 10^{-4} sec^{-1}$ at 80°). The spectrum in the δ2-3 region changed from one complex pattern to another, with no detectable doublet that could be attributed to the methylene protons of a cyclic diamide.

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The production of PhO^- in alkali was also followed at 287 nm with a Zeiss spectrophotometer, and the rate constant calculated from initial rates or from change of rate with time.

At 40° in 1 N NaOH, and taking $\epsilon^{287}_{PhO^-} = 2.58\times10^3$

$$k = dOD/dt)_{t=0} / \Delta OD_\infty = \frac{0.360-0.267}{140-40 \text{ min}} / \frac{1.15\text{mg} \times 2.58\times10^3}{216\text{mg/meq} \times 2.6\text{ml}}$$

$$= 1.75\times10^{-4}\text{min}^{-1}$$

Or, from change in rate with time

$$e^{k(t_2-t_1)} = dOD/dt)_{t_1} / dOD/dt)_{t_2}$$

$$= \frac{0.360-0.267}{140-40 \text{ min}} / \frac{1.273-1.232}{1280-1225 \text{ min}} = 1.25$$

$$k = 2.3 \log(1.25) /(1250-90 \text{ min}) = 1.92\times10^{-4} \text{ min}^{-1}$$

The agreement between the two methods of calculation is good. From similar calculations for other runs:

Rates of Hydrolysis of $H_2NCH_2CH_2NHPO_3^-Ph$ in Base

temp	solution	k (min^{-1})	time followed
40°	1 N NaOH	1.8×10^{-4}	5×10^3 min
40°	0.1 N NaOH	0.9×10^{-4}	5×10^3
24°	pH 10.4, I=0.8N	0.29×10^{-4}	2×10^3

The factor of two difference in rate between 1.0 N and 0.1 N NaOH could be an ionic strength effect ($k = 0.83\ e^{0.77\ I}$), but the data are too meagre to make much of. Adjusting the rate constant at pH 10.4 to take account of the protonation of the amine group (pK = 9.9) and of the 16° temperature difference indicates that the rate is independent of (OH^-).

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Phenyl N-methylethylenediaminephosphorodiamidate, Ph(MeHenePDA)

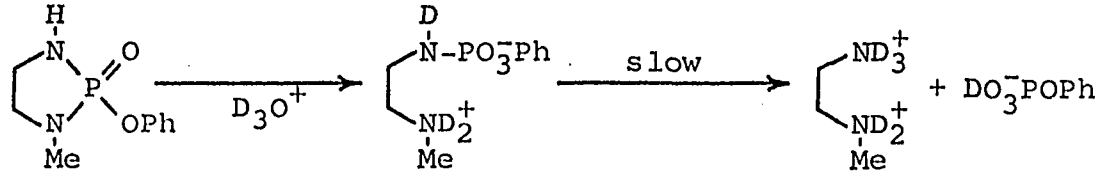
Reaction of N-methylethylenediamine (1.48 g, 20 mmole) and phenyl dichlorophosphate (2.11 g, 10 mmole) in dichloromethane (100 ml) gave, after filtration, an oil that sublimed at 100°, 10^{-5}mm. Resublimation gave 0.43 g (20% theory) white solid melting about 78°. The product is insoluble in CCl_4 and non-polar solvents.

IR 4 analysis
NMR 3

Ph(MeHenePDA) Hydrolysis Products

The UV spectral changes during hydrolysis show that ring-cleavage is occuring, but not which P-N bond is being cleaved. In order to determine that, the products were looked at by NMR.

The NMR spectrum of a solution of 53 μmole Ph(MeHenePDA) in 250 μl D_2O clearly showed the doublet due to the PNMe group. Addition of 5 μl 12 N HCl produced complete collapse of this doublet to a singlet by the time the next spectrum was recorded (5 min). A further slow reaction ($t_{1/2} \sim 7$ min in 1 N DCl) then produced the two singlets of the free diamine from the singlet and complex multiplet of the ring-opened product.



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Addition of Ph(MeHenePDA) to 1.1 equivalents of NaOD in D_2O gave a solution (0.5 N) whose NMR spectrum contained a complex multiplet for the methylene protons and a singlet which integrated for about 93% of the area expected for the methyl group. At least part of the missing 7% might be accounted for by exocyclic cleavage. Ring cleavage therefore proceeds predominently, if not entirely, by cleavage of the P-NMe bond.

Analysis of UV spectra to determine % PhO^-, in the same manner as was used for Ph(H_2enePDA), showed 5.9% at pH 10.5 and 11% in 0.025 N NaOD/D_2O.

Ph(MeHenePDA) Secondary Reactions

In acid, as mentioned above, the ring-opened product hydrolyzes with a half-time of about 7 minutes in 1 N DCl.

In base, the ring-opened product reacts to produce PhO^-. The solution used for product determination in base was kept at room temperature and its NMR spectrum recorded several times over a period of days.

Time	0 hr	7 hr	22 hr	53 hr	910 hr
Singlet Area	92.5%	88%	77%	69%	37%
PhO^-	<10%	14.5%	21%	42%	81%

Analysis of the data is difficult since the small excess of base would soon be used up by the secondary reaction; however, the secondary reaction in base seems to have a half-time on the order of 120 hours ($k \sim 2.1 \times 10^{-6} sec^{-1}$) at room temperature.

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Ph(MeHenePDA) Hydrolysis Rates

pH	Buffer Solution	I (M)	$t_{\frac{1}{2}}$ (sec)	k_2 ($M^{-1}sec^{-1}$)	temp. (°C)	
				acid		
6.41	phosphate	0.2	18	9.8×10^4	24.85	
7.03	"	0.2	77	9.55×10^4	20.0	
7.66	"	0.2	357	8.91×10^4	20.0	
8.80	0.02N NH_4^+	0.2	2900	15.1×10^4	30.1	
				base		
10.52	carbonate	0.2	495	2.14	30.0	a.
10.63	"	0.2	1260	0.84	20.0	a.
11.06	KCl	0.2	(114)	2.71	30.0	a., b.
11.51	KCl	0.2	(56)	1.95	30.0	a., b.
	0.01 N NaOH		28	2.47	30.0	
	0.1 N NaOH		5	1.38	24.85	
pD	D_2O					
				acid		
7.24	phosphate	0.2	42	2.9×10^5	30.0	
				base		
	0.01 N NaOD		37	1.82	19.95	
			32.3	2.14	"	
			24.1	2.87	30.0	
			25.3	2.74	"	
	0.0256N NaOD		9.8	2.8	29.85	

a. corrected for γ_{OH}
b. extrapolated to zero buffer (piperidine) concentration

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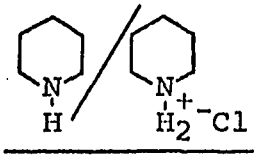
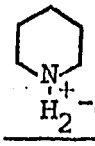
Ph(MeHenePDA) Buffer Catalysis

piperidine 		$t_{\frac{1}{2}}$ (sec)	k_1 (sec^{-1})
1 : 1	0.2 N	108	6.41×10^{-3}
pH 11.06	0.04	113	6.13×10^{-3}
3 : 1	0.2	50	1.38×10^{-2}
pH 11.51	0.04	55	1.26×10^{-2}

Ionic strength held constant at 0.2 N with KCl.
Temperature held at 30.0°.

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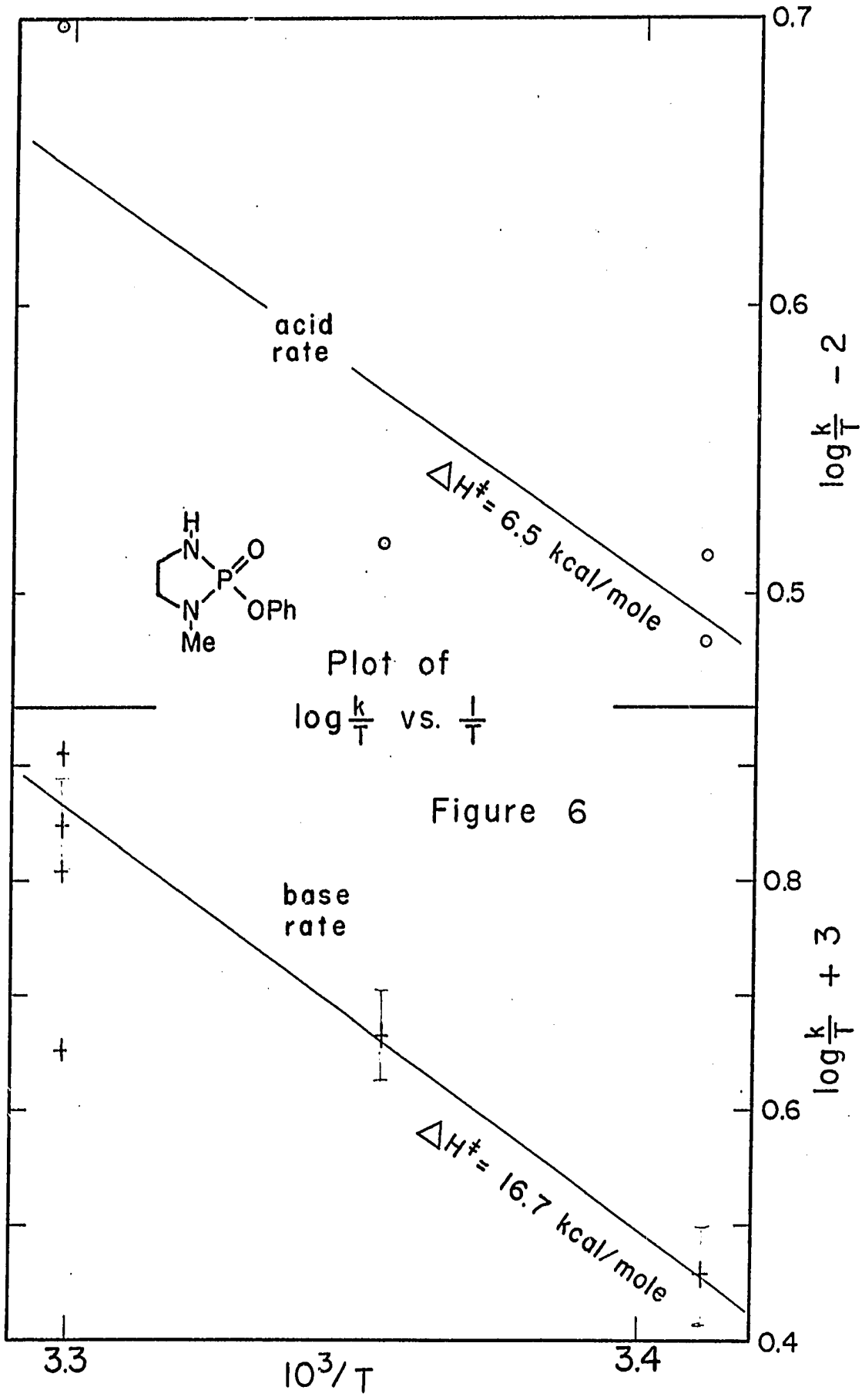

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N,N'-dimethylethylenediaminephosphorodiamidochloridate

Cl(Me_2enePDA)

Although this chloridate is mentioned in the literature[1], no experimental details for its preparation are given.

It was prepared in the expected manner by addition of N,N'-dimethylethylenediamine (8.8 g, 100 mmole) in 20 ml dichloromethane by syringe to phosphorus oxychloride (7.7 g, 50 mmole) in 80 ml dichloromethane with stirring and cooling in a serum capped flask. A copious white precipitate formed immediately. After addition was complete and the mixture had stood at room temperature for about 30 minutes, the white crystals were filtered under nitrogen and washed with dichloromethane. The solution was evaporated and the orange residue extracted with carbon tetrachloride. The soluble material was sublimed at 0.1 mm, 100°, giving 2.7 g (29% theory) of white solid, mp 74.5-75.5°. This melting point is considerably lower than that given by Utvary et al. (213-215°) and is more in line with the melting points of similar compounds. The high melting point given by Utvary might indicate hydrolysis of his melting point sample.

IR 5 NMR 4 analysis

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[1] K. Utvary, V. Gutmann, Ch. Kemenater, Inorg.Nucl.Chem.Lett., 1, 75(1965)

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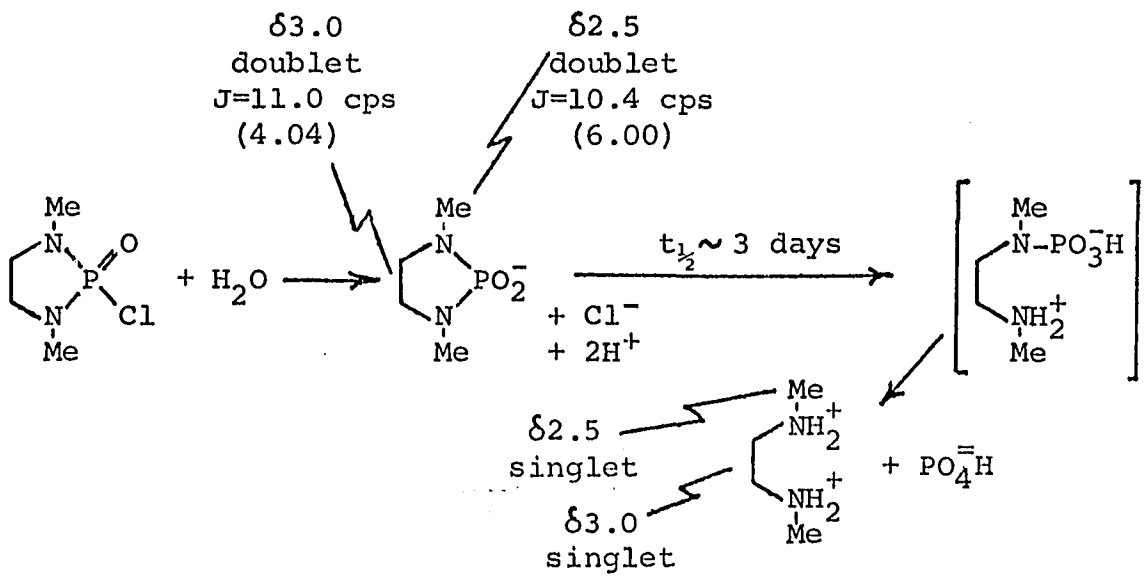
Cl(Me_2enePDA) Hydrolysis Products

The products of hydrolysis of the chloridate were investigated by NMR spectrometry. A total of 9.5 mg of the solid chloridate was added in portions to 4 ml water held at pH 10.1, 29°, in the pH-stat. Fisher 0.1 N NaOH was used as titrant. After the reaction was nearly complete (5 min after addition of the last portion of chloridate), the solution was evaporated to dryness under vacuum. The thin film of solid was dissolved in 0.46 g D_2O, and its NMR spectrum recorded.

The NMR spectrum showed two doublets in the integrated ratio of 3:2, indicating loss of chloride with preservation of the ring. Over a period of several days in the NMR tube the two doublets gradually disappeared (50% gone in 3 days) with the eventual appearance of two new singlets (67% appeared in 10 days). Too few spectra were taken to be able to get a recognizable spectrum of the presumed ring-open intermediate.



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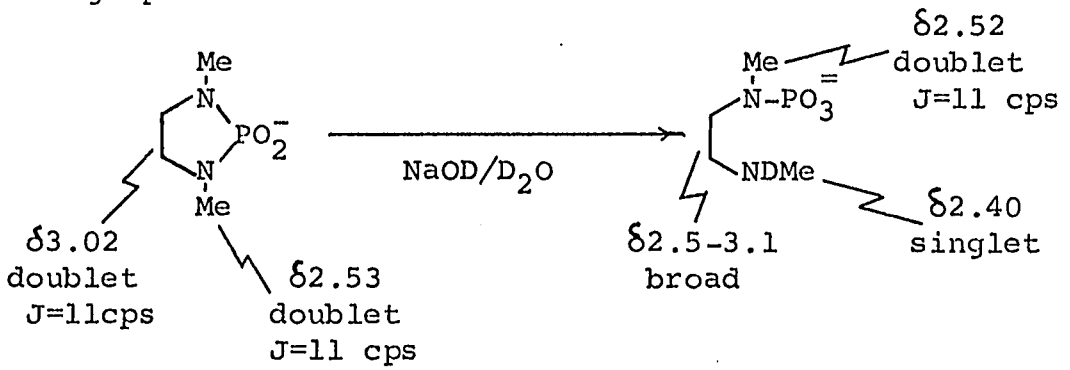
The ring-opened amide could be detected when the reaction solution was kept basic. Addition of 0.25 ml 3 N $NaOD/D_2O$ to 13 mg (0.077 mmole) of Cl(Me_2enePDA) in an NMR tube gave a solution whose NMR spectrum consisted of the two doublets of the cyclic diamide. Disappearance of these doublets was slow even on heating at 80° ($t_{1/2}$ ~ 50 hr at 80°). Analysis of the spectra was complicated by the overlapping of some product and starting material peaks and by leaching of the glass by alkali at that high a temperature (some precipitate formed in the NMR tube). However, after 79 hours at 80°, the solution gave a spectrum showing only the two doublets of cyclic diamide and the doublet, singlet, and broad multiplet of the ring-opened amide.



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Cl(Me_2enePDA) Hydrolysis Rates

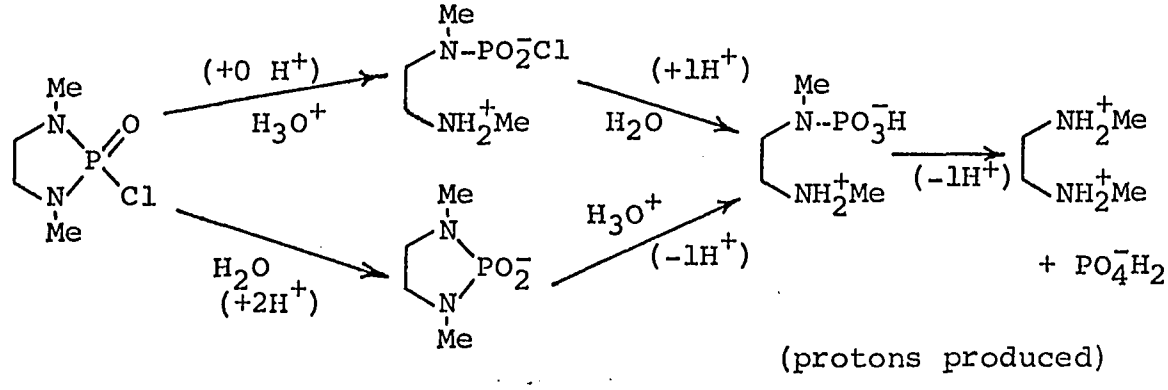
The rate of hydrolysis of the chloridate was followed in the pH-stat. The magnetically stirred solution was thermostatted at 29±1°, a few mg of the solid chloridate added directly to 4 ml water at the desired pH, and the uptake of 0.1 N NaOH recorded as a function of time. The data gave good first-order plots to about 5$t_{1/2}$'s.

Hydrolysis of Cl(Me_2enePDA) at 29°

pH	$t_{1/2}$	$\frac{(H^+) \text{ produced}}{PCl \text{ added}}$	k_1	$k_1 - k_o$
5.1	0.64 min	0.58	1.08 min^{-1}	0.647 min^{-1}
6.1	0.95	1.26	0.73	0.297
7.1	1.43	1.71	0.484	0.051
8.1	1.58	1.78	0.439	0.006
10.1	1.60	1.64	0.433	0.0

k_o = rate at pH 10

The results can be rationalized on the basis of a water rate (k_o) which produces two protons, an acid-catalyzed rate which produces no protons in the pH range 3-9, and a variety of secondary reactions.



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Although this scheme is reasonable and can be made to explain the variation in (H^+)-produced/PCl-added and the fact that k_1-k_o is not proportional to (H^+), it is all conjecture beyond the first step.

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Phenyl o-phenylenediaminephosphorodiamidate, Ph(H_2PhenePDA)

A sample prepared by F. Kerst [1] was used without further purification.

Ph(H_2PhenePDA) Hydrolysis Products

According to Kerst, in 50% DME-water, acid cleaves one P-N bond and base cleaves the P-OPh bond with preservation of the ring.

Ph(H_2PhenePDA) Hydrolysis Rates

Kerst ran the hydrolysis in 50% DME for solubility reasons, but the diamidate is slightly soluble in water. In order to have some idea of the effect of mixed solvents, the rates in water were measured.

The diamidate was added as a freshly prepared THF solution to the buffer solution thermally equilibrated in the Cary spectrophotometer. The final THF concentration was less than 2%. The change in OD at 290 nm was followed for over 6$t_{\frac{1}{2}}$'s and the half-times determined. Buffer catalysis was observed on dilution.

From dilution of I = 0.2 N phosphate (pH 7.63 at 25°) with I = 0.2 N $NaClO_4$, the rates at 30° fit the expression:

$$k_{obs} = 1.5\times10^{3}(OH^-) + 7\times10^{4}(P_i)(OH^-) \ , \ sec^{-1}$$

(P_i) = 0.073 M for I=0.2N P_i, $(OH^-) = 10^{pH-13.83}$

[1] A. F. Kerst, Ph.D. Thesis, Harvard University, 1967

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From dilution of 3:1, 1:1, and 1:3 tris:tris-$HClO_4$ buffers with $NaClO_4$, I = 0.2 N, the rates at 30° fit the expression:

$$k_{obs} = (1.0 \pm 0.2) \times 10^{3} (OH^-) + (0.11 \pm 0.01)(\text{tris}), \quad sec^{-1}$$

$$(OH^-) = 10^{pH-13.83}$$

And in acid:

Ph(H_2PhenePDA) Acid-Catalyzed Hydrolysis, 30°

solution	$t_{1/2}$	k_{H^+}
0.2 N $HClO_4$	3.4 sec 3.2-3.4	1.02 $M^{-1}sec^{-1}$ 1.02-1.08
0.1 N $HClO_4$ +0.1 N $NaClO_4$	7.0	0.99
0.01 N $HClO_4$	56.4	1.23
+0.19 N $NaClO_4$	52.5	1.32
0.01 N HCl +0.2 N KCl	56.5	1.23

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Phenyl N,N'-dimethylethylenediaminephosphorodiamidate,

Ph(Me_2enePDA)

Reaction of N,N'-dimethylethylenediamine (4.4 g, 50 mmole) with phenyl dichlorophosphate (5.3 g, 25 mmole) in dichloromethane gave 3.6 g (90% theory) of filterable diamine dihydrochloride. Vacuum sublimation of the soluble material gave 3.1 g of solid contaminated with diamine dihydrochloride. The solid was purified by dissolving it in 50 ml CCl_4, washing with 1 ml 0.1 N NaOH, drying the solution with Na_2SO_4, and resublimation.

The resublimed white crystalline solid (2.6 g, 46% theory) melted at 58.5-61.0°. It was soluble in chloroform, carbon tetrachloride, and polar solvents; insoluble in hydrocarbon solvents and ether.

IR	UV
NMR	analysis

Ph(Me_2enePDA) Hydrolysis Products

In acid, the first reaction is opening of the ring by cleavage of one P-N bond . The hydrolysis of the second P-N bond is detectably slower. By taking NMR spectra of a solution of 0.14 mmole PDA in D_2O after addition of 5 µl 12 N HCl, both reactions could be observed.

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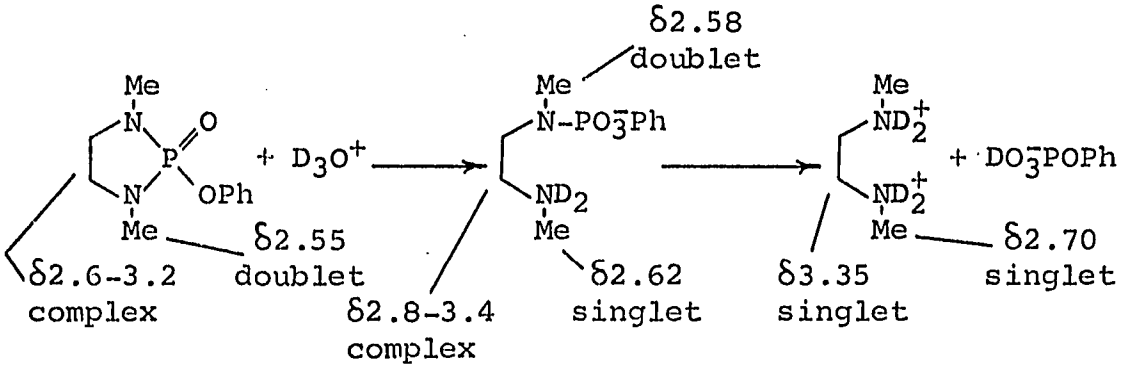

The UV spectral changes fit this scheme quite well. The PDA was hydrolyzed at pH 6.4 and in 0.1 N HCl, the solutions quenched with base, and the UV spectra recorded.

	max	min	max	min	max		
λ	255	257	260	264	266	nm	Ph(Me$_2$enePDA)
ε	268	264	328	216	254		2×10^{-3} N in water

	shldr	max	shldr		
λ	257	262	266	nm	pH 6.4 14 hr hydrolysate;
ε	391	487	428		in 0.1 N NaOH

	shldr	max	min	max	shldr		
λ	258	262	264	267	272	nm	0.1 N HCl ½hr hydrolysate;
ε	550	708	697	726	510		in 0.1 N NaOH

Fourteen hours at pH 6.4 at room temperature corresponds to 2-2.5 half-times for the first hydrolysis, so the spectral growth is only about 80% complete. In 0.1 N HCl, on the other hand, the first reaction is over almost instantly, and the secondary reaction (assuming a $t_{\frac{1}{2}}$ on the order of 10 min) will be nearly complete in ½ hour.

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In base, Ph(Me_2enePDA) hydrolyzes to give about 5% PhO^- and 95% ring-opened amidate. This is seen most clearly in the NMR spectrum. In molar NaOD, the NMR spectrum shows the doublet of the starting material PNMe group slowly diminishing while a new doublet 0.05 ppm downfield and a singlet 0.4 ppm upfield grow. A trace of phenoxide signal around δ6.5 also appears.

The UV spectral changes parallel those for Ph(H_2enePDA). Subtracting the absorption due to PhO^- (Figure 2) leaves the spectrum of the ring-cleaved amidate (Figure 7).

	shldr	max	shldr	
λ	257	262	267	nm
ϵ	428	525	460	

Ph(Me_2enePDA)
5 N NaOH hydrolysate
PhO^- absorption subtracted

The percentage of exocyclic cleavage was not investigated systematically, but seems to be rather insensitive to changes in pH, temperature, and ionic strength.

Exocyclic Cleavage in Ph(Me_2enePDA) Hydrolysis

solution	temp	% phenoxide (UV)
0.1 N NaOH	25.3°	5.2
+0.4 N NaCl	"	5.5
+0.9 N NaCl	"	5.0
1.0 N NaOH	"	5.2
1.0 N NaOH	30°	4.3
1.0 N KOH	59.1°	6.8
0.9 N NaOD/D_2O	30°	5.9
0.1-1 N NaOD/D_2O	room temp	5 (NMR)

The % PhO^- was calculated in a similar manner to that used in the case of Ph(H_2enePDA) hydrolysis, p 25, but using ϵ^{262}= 525 for $RNMePO_3^-Ph$.

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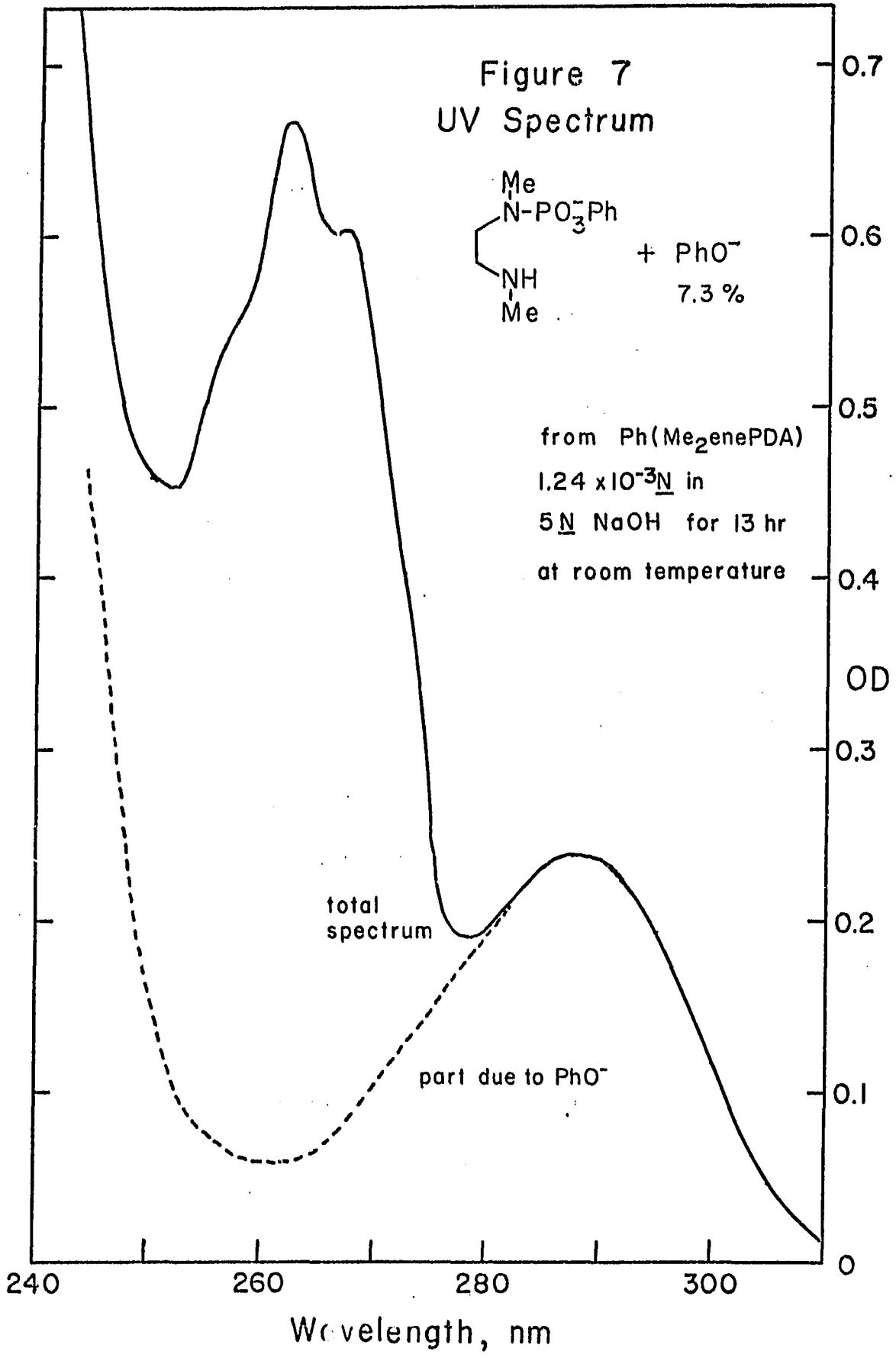

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Ph(Me_2enePDA) Hydrolysis Rates

pH	Buffer Solution	I (M)	$t_{1/2}$ (sec)	k_2 ($M^{-1}sec^{-1}$)	temp. (°C)
				acid	
3.57	formate	0.2	34	75.9	20.0
3.67	0.05N formate	0.2	23.5	138	30
	0.1N "	0.2	27.5	118	30
	0.2N "	0.2	23.6	137	30
	1.0N "	1.0	13.7	237	30
4.12	0.05N acetate	0.5	83	110	25.0
4.14	0.5 N acetate	0.5	94	102	25.0
4.34	0.2 N "	0.2	250	60.3	20.0
4.45	0.2 N "	0.2	124	159	30.0
4.60	0.05N "	0.5	259	111	25.0
4.61	0.2 N "	0.5	264	107	25.0
4.65	0.5 N "	0.5	284	111	25.0
4.94	0.2 N "	0.2	850	70.8	19.9
4.94	0.04N "	0.2	330	183	39.7
			230	260	49.4
5.05	0.2 N "	0.2	580	135	30.0
5.10	0.05N "	0.5	768	114	25.0
5.12	0.2 N "	0.5	810	114	25.0
5.19	0.5 N "	0.5	828	130	25.0
5.49	0.2 N "	0.2	1600	135	30.0
6.44	phosphate	0.2	1.46×10^4	132	29.95
10.4	methylamine	0.2	$>1.7 \times 10^6$	less than 10% reaction in 73hr at room temp.	

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Buffer Solution	$t_{1/2}$, (sec)	$10^4 k_2$, ($\underline{M}^{-1}sec^{-1}$) base	temp.
0.1 N NaOH	9.3×10^4	0.75	25.3°
0.1 N NaOH + 0.4 N NaCl	9.8×10^4	0.71	25.3
0.1 N NaOH + 0.9 N NaCl	10.2×10^4	0.68	25.3
1.0 N NaOH	9.0×10^3	0.77	25.3
"	5.6×10^3	1.23	30.0
"	2.43×10^3	2.85	39.9
1.0 N KOH	667	10.4	59.1
D_2O			
0.9 N NaOD	5.6×10^3	1.36	30.0
1.24 N NaOD	2.04×10^3	2.72	39.9
0.25 N NaOD + 0.75 N NaCl	a)	0.33	room temp.
0.5 N NaOD + 0.5 N NaCl	a)	0.42	"
1.0 N NaOD	a)	0.42	"

a) Obtained by NMR. Data plotted as second-order reaction to 75% completion to obtain k_2. Initial PDA concentration ~0.15N.

Formate Buffer Catalysis

Sodium formate was added to 0.5N 1:1 acetate buffer in varying concentrations. Ionic strength was held constant with NaCl at 1.5N.

pH	Formate Conc.	$t_{1/2}$	$k_1/(H^+)$, 25.0°C
4.51	0.0 N	190 sec	1.18×10^2 $\underline{M}^{-1}sec^{-1}$
4.71	0.5 N	194	1.85×10^2
4.88	1.0 N	195	2.7×10^2

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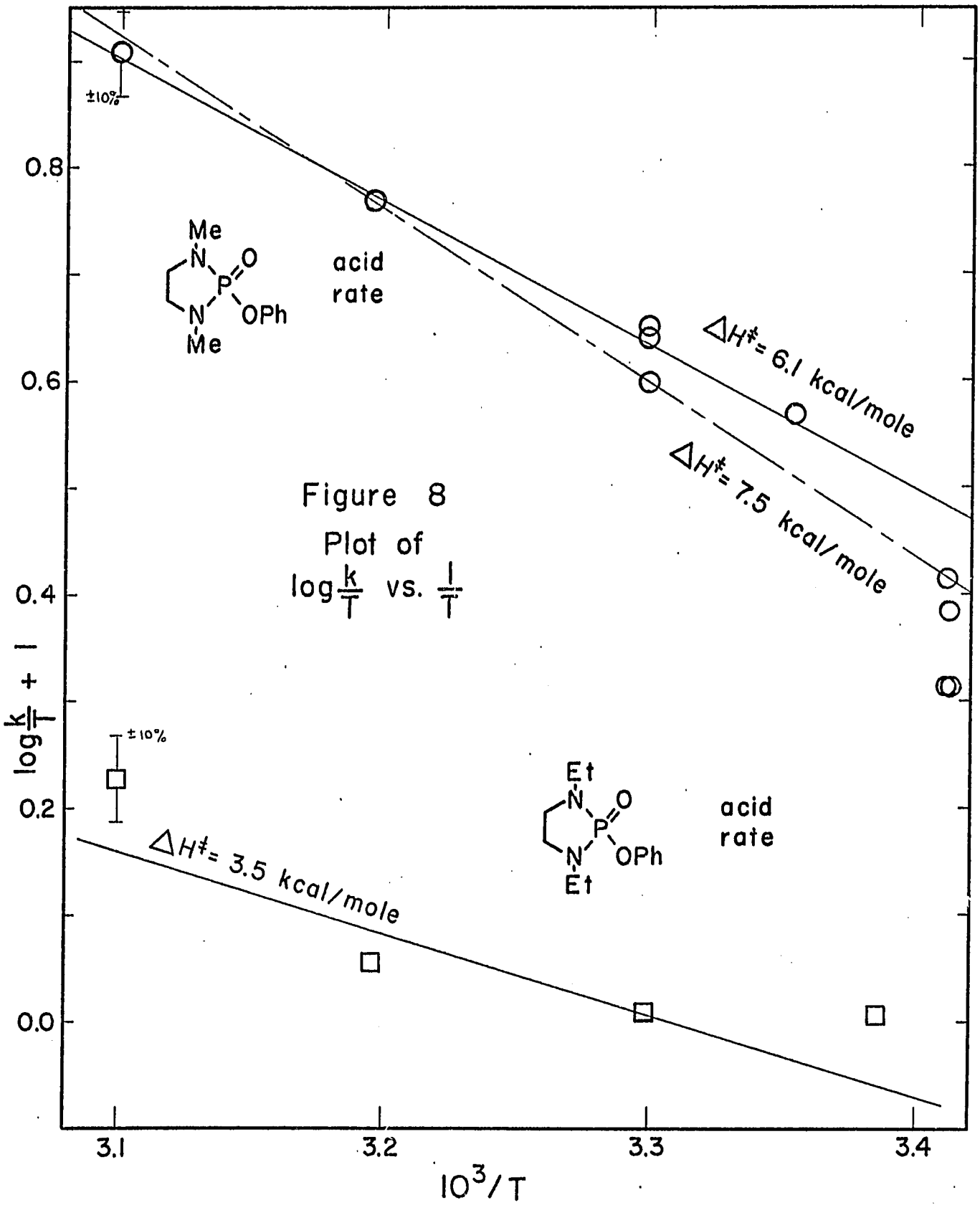

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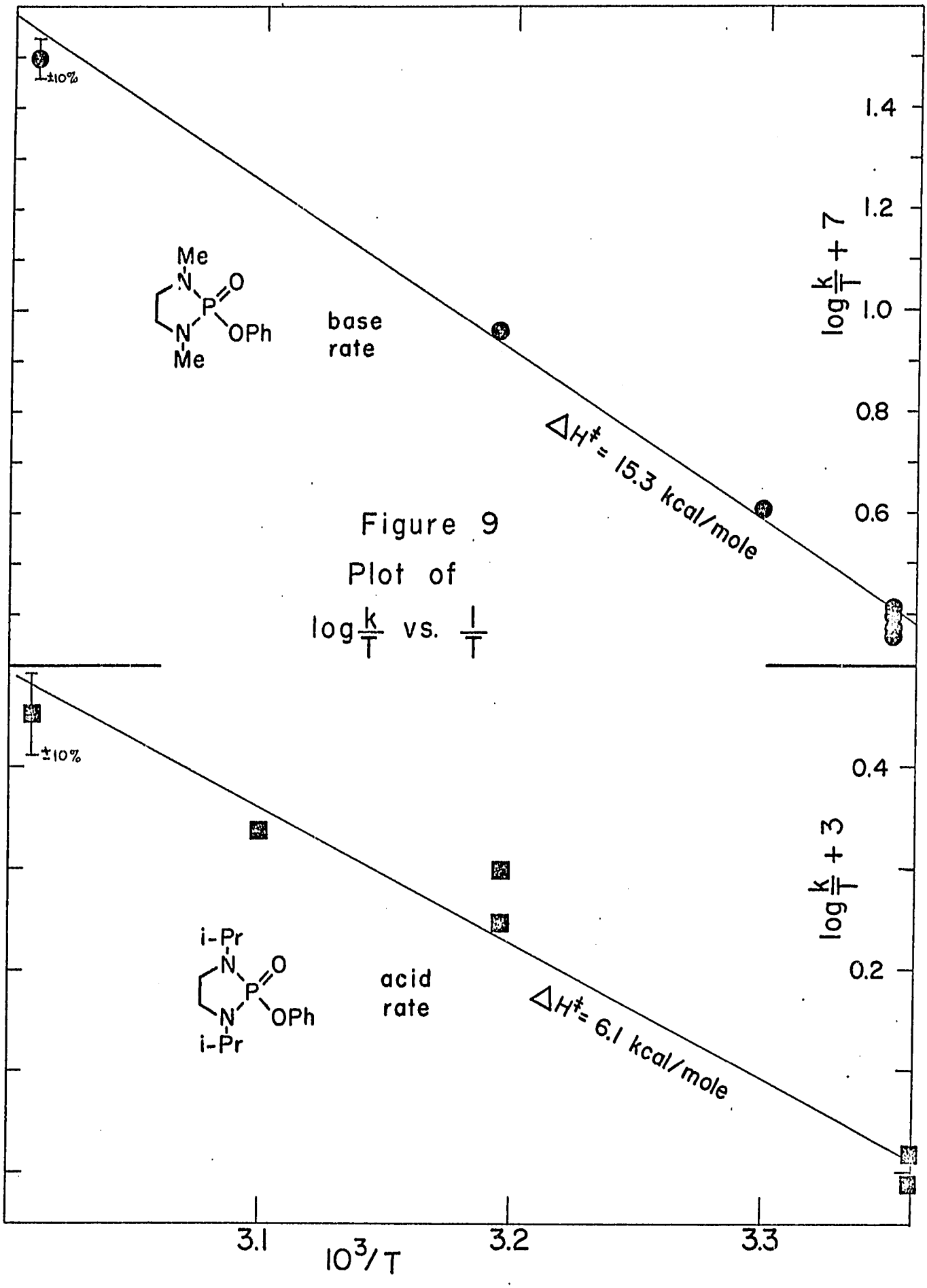

Figure 9
Plot of
$\log \frac{k}{T}$ vs. $\frac{1}{T}$

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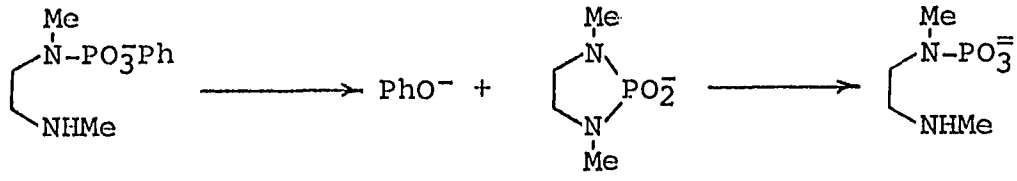
Ph(Me_2enePDA) Secondary Reactions

As mentioned during the discussion of products, the ring-opened product hydrolyzes in acid to yield phenyl phosphate and the free diamine.

In alkaline solution, the ring-opened product recloses the ring with loss of phenoxide ion.



A mixture of 32 mg Ph(Me_2enePDA), 0.13 g 10 N NaOD, and 0.18 g D_2O in an NMR tube was heated and shaken for ½ hr until a homogeneous solution formed. Heating was continued at 80° and NMR spectra recorded at intervals. The spectra showed the dissappearance of the ring-opened amidate and the production of PhO^- with a half-time of about 22 hours ($k_1 = 0.9 \times 10^{-5} sec^{-1}$ at 80°). The two doublets of the cyclic diamide were clearly distinguishable; but, since there was not a large excess of base present, the doublets reached a maximum at about 40 hours and then were gradually replaced by the two singlets of free diamine (see Cl(Me_2enePDA) HydrolysisProducts).

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Phenyl N,N'-diethylethylenediaminephosphorodiamidate Ph(Et_2enePDA)

Phenyl dichlorophosphate reacts more slowly with N,N'-diethylethylenediamine than with the lower diamines, as judged by the rate of precipitate formation. The crude reaction product gradually turned orange, probably due to air oxidation of some impurity. Distillation at 10^{-5} mm, 80°, gave a mobile liquid which solidified in the freezer and melted slightly above room temperature. The distilled product turned slightly orange on standing, and its melting point dropped to below room temperature.

A sample of analytical purity was prepared by treating an ether solution of the PDA with calcium hydride, filtering, and redistilling at 0.1-0.2 mm, 110-120°. IR . NMR analysis

Ph(Et_2enePDA) Products

The UV spectral changes in acid and base parallel those for the other PDA's, so it is assumed that the corresponding products are formed. In 1 N KOH at 80°, 6.1% phenoxide was produced in the primary reaction.

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Ph(Et_2enePDA) Hydrolysis Rates

pH	solution	I	$t_{1/2}$	temp	k_2 acid
3.67	formate	0.2 N	112 sec	30.0°	28.8 $M^{-1}sec^{-1}$
4.45	acetate	0.2	630	30.0	30.9
4.94	acetate	0.2	1700	39.7	35.5
	(0.04N)		1100	49.4	54.5
6.44	phosphate	0.2	$8.43x10^4$	22.4	29.9
					base
	1.0 N NaOH	1.0	$3x10^5$	30	$2x10^{-6}$
	1.0 N KOH	1.0	$5x10^3$	69.2	$1.4x10^{-4}$

Rate constants were obtained from Guggenheim plots.

Ph(Et_2enePDA) Secondary Reaction

A solution of 4.25 mg PDA in 50 ml 1 N KOH heated in a Kerst tube for several weeks at 80° produced 94.6% of the total PhO^- absorption expected with a half-time of 77.8 hours ($k = 2.5x10^{-6}sec^{-1}$).

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Phenyl N,N'-di-isopropylethylenediaminephosphorodiamidate

Ph(i-Pr_2enePDA)

The procedure of W. R. Boon[1] was used to prepare N,N'-di-isopropylethylenediamine.

$$5\ \underline{i}\text{-}PrNH_2 + BrCH_2CH_2Br + 3\ H_2O \xrightarrow[\text{reflux}]{} \underline{i}\text{-}PrNHCH_2CH_2NH\text{-}\underline{i}\text{-}Pr$$

30 g 19 g 5.4 g 15 hrs 6 g (41% theory)

After the reaction mixture had refluxed overnight, it was treated with 9 g NaOH and the excess i-$PrNH_2$ distilled. The remaining liquid was decanted and the solid washed with ether. The combined liquid was distilled from NaOH, the solid material (mp > 30°) which distilled at 60°, 30 mm, presumably being a hydrate of the desired product. All the potential product was washed into a flask with ether and dried overnight with CaH_2. The resulting solution was distilled at aspirator pressure to give 6.0 g of product.

The diamidate was prepared by mixing the diamine (2.9 g, 20mmole) and phenyl dichlorophosphate (2.1 g, 10 mmole) in benzene (80 ml) in a serum capped flask. The solution turned milky after mixing, but was heated overnight at 40-60° anyway. Filtration gave 2.1 g (97% theory for dihydrochloride) white solid. The benzene was removed under vacuum and the oily residue sublimed at less than 150°, 0.05-0.1 mm, as clusters of white needles, 2.4 g (85% theory), mp 44-48°.

IR NMR UV analysis

1 W. R. Boon, J.Chem.Soc., 314(1947)

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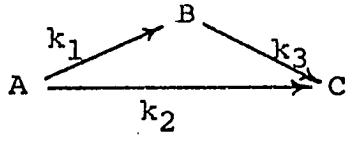
Ph(i-Pr$_2$enePDA) Hydrolysis Rates

The reaction of the PDA in acid was followed by the increase in OD at 265 nm.

solution	$t_{1/2}$	temp	k_2
0.1 N HCl	22 sec	room temp (24.5°)	0.31 $M^{-1}sec^{-1}$
0.01 N HCl	220-238	"	0.29-0.31
0.01 N HCl	112-125	39.7	0.55-0.62
+0.2 N KCl	99	49.4	0.70
	74	59.1	0.94

Measurement of the base-catalyzed hydrolysis rate was complicated by the fact that the secondary reaction of the ring-opened product was occurring at a comparable rate. The production of phenoxide ion in 1 N KOH and in 0.2 N KOH + 0.8 N KCl was followed by the increase in OD at 287 nm for samples withdrawn from Kerst tubes thermostatted at 87°. The resulting data from hydrolysis in 1 N KOH could be analyzed graphically to give two half-times, 192 and 54.3 hr ($k' = 3.61 \times 10^{-3}$ hr^{-1}, $k = 1.28 \times 10^{-2} hr^{-1}$). For a more accurate analysis, or at least a less biased curve-fitting, the data were least-squares fitted by computer to a scheme of the sort



A = Ph(i-Pr$_2$enePDA)
B = i-PrNHCH$_2$CH$_2$NPO$_3^-$Ph (i-Pr)
C = PhO$^-$

For the computer program used, see appendix I. A plot of OD^{287} vs. time for these two base concentrations is given in Figure 10.

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The results from the computer are quite satisfying:

Hydrolysis of Ph(i-Pr_2enePDA) in Base, 87°

(KOH)	k_1, hr^{-1}	k_2, hr^{-1}	k_3, hr^{-1}	$OD^{287}/ OD^{287}_{calc}$
1.0 N	1.33×10^{-2}	6.7×10^{-3}	3.78×10^{-3}	91%
0.2 N	2.34×10^{-3}	1.6×10^{-3}	3.73×10^{-3}	95%

Ph(i-Pr_2enePDA) Secondary Reaction

The k_3 determined above in 1 N and 0.2 N KOH is supposed to be the rate of reaction of the ring-opened amidate. To check this, k_3 was measured separately. The ring-opened amidate was prepared by adding 2.5 µl of 0.1 N HCl to a solution of 10.2 mg PDA in 0.25 ml D_2O in an NMR tube and allowing the mixture to stand at room temperature for three hours (=5$t_{\frac{1}{2}}$'s for hydrolysis at 10^{-3}N H^+). The NMR spectrum of the solution then showed two (amide and ammonium) approximately equal doublets for the methyl groups of the i-propyl groups. This solution was then added to 50 ml 1 N KOH, sealed in a Kerst tube, heated at 87°, and the appearance of PhO^- absorption at 287 nm followed. Least-squares fitting the data with the computer (Appendix I) gave $k_3 = 3.89 \times 10^{-3} hr^{-1}$, $OD_\infty = 1.63$ (88% theory). The agreement with the value from the three parameter equation ($k_3 = 3.75 \times 10^{-3} hr^{-1}$) is very good.

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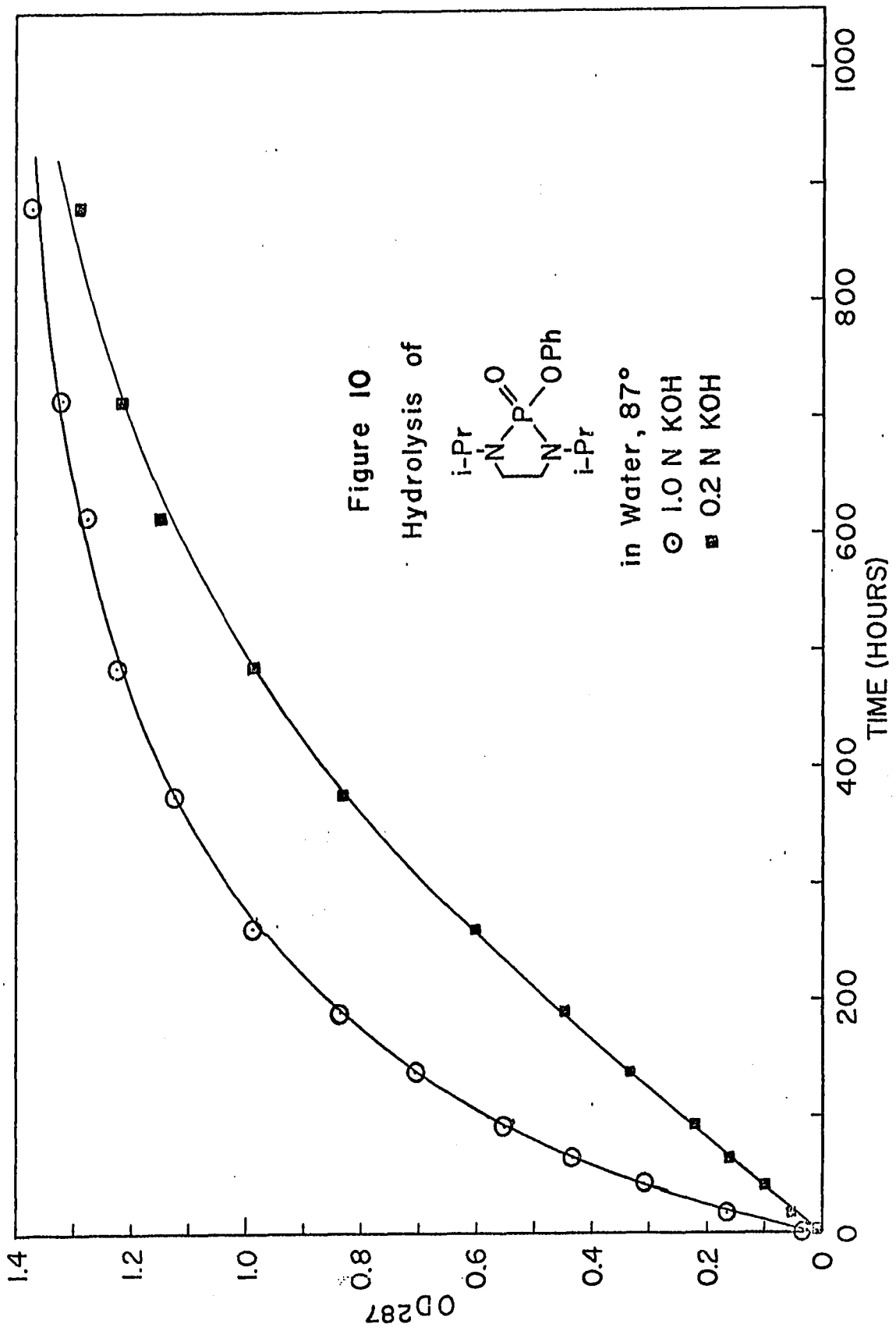

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Phenyl N,N'-di-t-butylethylenediaminephosphorodiamidate, Ph(t-Bu_2enePDA)

N,N'-di-t-butylethylenediamine was prepared in the same manner as was the di-i-propyl derivative[1]. After addition of NaOH and distillation of excess t-$BuNH_2$, the product separated from the aqueous layer as an orange organic layer. Two distillations at reduced pressure from NaOH flakes gave 5.9 g (67% theory) colorless liquid bp 55°, 0.5 mm (lit.[1] bp 196-198°, 760 mm).

A mixture of N,N'-di-t-butylethylenediamine (1.72 g, 10 mmole) and phenyl dichlorophosphate (1.05 g, 5 mmole) in benzene (60 ml) showed no signs of reaction at room temperature. Refluxing for two hours gave a milky solution from which was filtered 1.9 g of solid wet with benzene. Evaporation of the benzene solution under reduced pressure and extraction of the resulting white solid with CCl_4 gave 1 g of crude product soluble in CCl_4, benzene, methanol, and slightly soluble (about 10^{-3}N) in water. The product sublimed at 120°, 0.5 mm, to give 0.8 g (52% theory) white powder, mp 117.5-119.2°.

IR	UV
NMR	analysis

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[1] W. R. Boon, J.Chem.Soc., 314 (1947)

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Ph(t-Bu_2enePDA) Hydrolysis Rates

A methanol solution of 11.3 mg PDA was dissolved in 50 ml 1 N HCl to give a 7.3×10^{-4} N solution. Two ml portions were sealed in glass ampules under vacuum and used for kinetic runs at two temperatures. At intervals a tube was taken from the thermostatted bath, broken open, and the UV spectrum from 230-320 nm recorded, both before and after addition of base (0.16 g 10 N NaOH / 1.16 g solution).

At 55° in 1 N HCl, hydrolysis to phenyl phosphate and diamine dihydrochloride occurred fairly rapidly, then the phenyl phosphate hydrolyzed to phenol and phosphoric acid. The spectra in base of the hydrolysis samples showed growing PhO^- absorption at 234 and 287 nm. Assuming first-order production of phenol, and knowing the initial PDA concentration, a rate constant of about $5 \times 10^{-7} sec^{-1}$ ($t_{1/2} \sim 400$ hr) can be calculated from the rate of phenol production after an initial induction period. From the increase in OD at 267 nm (the λ_{max} of $PhOPO_3^{=}$) during this induction period, after subtracting the absorption due to PhO^-, the initial reaction was found to have a half-time of 3.5 hours ($k = 5.5 \times 10^{-5} sec^{-1}$ at 55°).

At 30.5° the hydrolysis to phenol was too slow to be measured in 200 hr, but the initial reaction could be followed easily. First-order plots for several different OD changes

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gave $t_{1/2}$ = 20-40 hr ($k = 0.5\text{-}1.0 \times 10^{-5} sec^{-1}$ at 30.5°). The UV spectra after 160 and 210 hr were qualitatively the same as that of phenyl phosphate, although the calculated ε's differ by 10-20%. Thus, hydrolysis involves cleavage of both P-N bonds.

		λ	ε	λ	ε
hydrolysate	in acid	261 nm	410	265 nm	320
	base	262 nm	570	267 nm	580
$PhOPO_3H_2$	in acid	261 nm	360	266 nm	280
	base	263 nm	670	267 nm	690

The large variation in the calculated $t_{1/2}$ for hydrolysis at 30° might be at least partly due to the rate of hydrolysis of the ring-opened amidate to phenyl phosphate being comparable to the rate of hydrolysis of the PDA. A simple first-order analysis is then not applicable, and will give different "$t_{1/2}$'s" at different wavelengths. More evidence on this point is given in the discussion section.

The base-catalyzed hydrolysis of Ph(t-Bu_2enePDA) was too slow to be observed. A solution of 2.4 mg PDA in 0.1 g MeOH was mixed with 5.8 g 1 N KOH and sealed in a teflon-lined brass tube. The tube was heated at 110-115° for 25 days. The UV spectrum of the solution showed no changes attributable to hydrolysis; in particular, $\Delta OD^{287} < 0.01$. Thus,

$$k < (0.01 / 2\times10^{6} sec)/(2.58\times10^{3} \times 2.4mg/310mg/meq \times 5.8ml)$$

$$= 1.3 \times10^{-9} sec^{-1}$$ for PhO^- production at 110° in 1N KOH.

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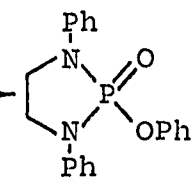
Phenyl N,N'-diphenylethylenediaminephosphorodiamidate, Ph(Ph_2enePDA)

N,N'-Diphenylethylenediamine was prepared by heating aniline (0.4 mole) and dibromoethane (0.1 mole) under nitrogen on a steam bath for an hour [1]. The crude product was extracted from aniline hydrobromide with CCl_4, and solvent and other volatiles removed under vacuum. The crude diamine was used without further purification.

$$BrCH_2CH_2Br + 4\ PhNH_2 \xrightarrow[100^\circ,\ 1\ hr]{N_2} PhNHCH_2CH_2NHPh + 2\ PhNH_3Br$$

$$\underset{3\ mmole}{PhNHCH_2CH_2NHPh} + \underset{3\ mmole}{Cl_2\overset{O}{\overset{\|}{P}}OPh} \xrightarrow[\underset{15\ ml}{PhBr,\ reflux}]{N_2} \text{[diamidate]} + 2\ HCl$$



A mixture of N,N'-diphenylethylenediamine and phenyl dichlorophosphate in bromobenzene was refluxed several hours until the solution turned clear. Removal of bromobenzene under vacuum left a light-brown powder which was purified by dissolving it in dioxane, passing the solution through a short column of Woelm neutral alumina to decolorize it, and precipitating the product by adding water. Several more precipitations from dioxane with water and drying in vacuum gave a white solid, mp 190.1-191.6°, soluble in dioxane, THF, $CHCl_3$, CH_2Cl_2, and alcohol; but practically insoluble in water and CCl_4.

IR NMR UV analysis

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1 Beilstein, "Organische Chemie" 12 p.543

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Ph(Ph_2enePDA) Hydrolysis Products

In alkali, the PDA seems to undergo predominently exocyclic cleavage. The UV spectral changes are not diagnostic, since the absorption due to the PhO group is generally overpowered by that due to the two PhN groups. During hydrolysis, the peak at 243 nm decreases by about 20% while a longer-wavelength peak at 282 nm ($\epsilon \sim 3.7 \times 10^3$) grows. In an attempt to cancel the absorption due to the PhN groups, the difference spectrum of the hydrolysis mixture at pH 13 vs the hydrolysis mixture at pH 6 was recorded. If exocyclic cleavage had occurred, this procedure should give the difference spectrum of PhO^- vs. PhOH. And as expected, the difference spectrum showed positive peaks at 245 and 287 nm, and a negative peak at about 267 nm (which grew positive as the phosphoramide hydrolyzed in the acid solution).

For a more positive identification, the products were looked at by NMR spectroscopy. A solution of 30 mg Ph(Ph_2enePDA) in 3 g i-PrOH + 3 g 1 N KOH was sealed in a teflon-lined brass tube and heated at 110° for 45 hours (>10$t_{\frac{1}{2}}$'s). The solution was then cooled, partially neutralized with 12 N HCl, and evaporated. The NMR spectrum in D_2O showed the peaks at δ6.6 (3.1 protons) for 3 of the 5 PhO^- protons, a multiplet at δ6.8-7.4 (12.8 protons) for the other 12 aromatic protons, and a doublet (J = 8 cps, 3.1 protons) at δ3.6 for the 4 methyl-

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ene protons. The solution was quite dilute, so the integration was rather inaccurate, but it does show that hydrolysis in base proceeds predominently with exocyclic cleavage.

In acid solution, both P-N bonds seem to be hydrolyzed. The strong absorption in the UV spectrum at 240 nm slowly disappears in acid. Since this peak is due to PhNP [2,3] while $PhNH_3^+$ absorbs only weakly in that region (ϵ=169 at 254 nm [2]), both P-N bonds must be hydrolyzing.

---

[2] J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall, Englewood Cliffs, N.J. 1965, p 18

[3] A. F. Kerst, Ph.D.Thesis, Harvard University, 1967

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Ph(Ph_2enePDA) Hydrolysis Rates

Hydrolysis in acid was followed by the decrease in OD at 240 nm. The buffer solutions were equilibrated at 40° in the Zeiss spectrophotometer, and 10 µl of a solution of 1 mg Ph(Ph_2enePDA) in 1 ml methanol was added to start the reaction.

Hydrolysis of Ph(Ph_2enePDA) in Acid, 40°

solution	$t_{1/2}$	10^5 k
0.1 N HCl + 0.9 N KCl	92 min	12.6 sec^{-1}
0.33 N HCl + 0.67 N KCl	48 min	24.1
1.0 N HCl	20	57.8
1.0 N KCl	278	4.16
0.33 N KCl	492	2.35
0.9 N $NaClO_4$ + 0.1 N KCl	no change in 1500 min	
0.5 N HCl + 0.5 N $HClO_4$	18.4	62.8
1.0 N $HClO_4$	18.5	62.5

The PDA seems to be undergoing Cl^- catalyzed reaction as well as acid-catalyzed hydrolysis; however, the non-linearity of the Cl^- catalysis in (Cl^-) is extremely suspicious. This point needs further study.

The rate of hydrolysis of Ph(Ph_2enePDA) in base was measured by following both the decrease in OD at 242 nm and the increase in OD at 282 nm. Complications such as the low solubility of the PDA and the ready air oxidation of aromatic

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amines make the results very inaccurate, but at 80° in 0.2 N NaOH, 20% MeOH/H_2O, the hydrolysis seemed to have a half-time of about 2 hours (k_2= 5 x10^{-4} $\underline{M}^{-1}$$sec^{-1}$ at 80°). Similarly, at 61° in 1.0 N NaOH, 50% MeOH/H_2O, a Guggenheim plot of the first half-life's OD change at 283 nm gave k_2= (0.6-1.0)x$10^{-4}$$sec^{-1}$$\underline{M}^{-1}$.

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Phenyl N,N'-diphenylphosphorodiamidate, $Ph(Ph_2PDA)$

The material prepared by Kerst[1] was used without further purification.

$Ph(Ph_2PDA)$ Hydrolysis Products

According to Kerst, the dianilide hydrolyzes in aqueous base to PhO^- and $(PhNH)_2PO_2^-$.

$Ph(Ph_2PDA)$ Hydrolysis Rates

The rates of hydrolysis of the PDA in aqueous base were measured by following the increase in OD at 285 and 290 nm in the Zeiss spectrophotometer at 40.0°. There was noticeable OD_∞ drift, possibly due to air oxidation , but subtracting this drift by extrapolation gave good first-order plots for about $5t_{1/2}$'s.

$Ph(Ph_2PDA)$ Hydrolysis in Base, 40°

solution	$t_{1/2}$ 285nm	$t_{1/2}$ 290nm
1.0 N NaOH	32.2 min	31.7 min
0.3 N NaOH + 0.7 N $NaClO_4$	40.0	39.5
0.1 N NaOH + 0.9 N $NaClO_4$	61.0	61.7

An analysis of these rates is given under the heading Phosphoramidate Acidity.

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[1] A. F. Kerst, Ph.D. Thesis, Harvard University

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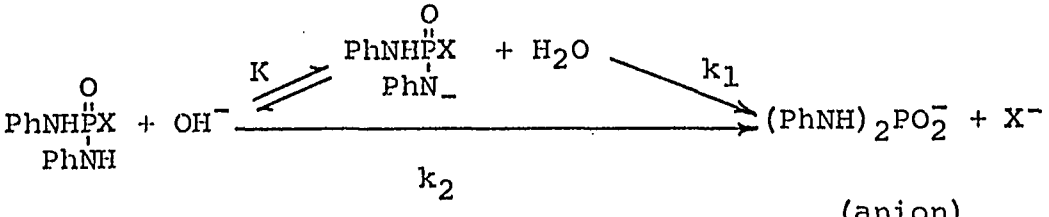
Phosphoramidate Acidity

The metaphosphoramidate pathway for phosphoramidate hydrolysis involves ionization of a PN-H proton, so it would be helpful to know the pK of such a group. Kerst observed that the calculated second-order rate constant for alkaline hydrolysis of $Ph(Ph_2PDA)$ begins to fall off at high (OH^-) [1]. A similar effect was observed by Coult and Green in the alkaline hydrolysis of p-nitrophenyl phosphorodianilide [2]. In both cases the proposal was made that this fall-off is due to ionization of an amide hydrogen, but the data were not analyzed from this point of view.



$$K = \frac{(anion)}{(amide)(OH^-)}$$

$$\frac{1}{k_{obs}} = \frac{K}{k_1K+k_2} + \frac{1}{k_1K+k_2} \cdot \frac{1}{(OH^-)}$$

Thus, a plot of $1/k_{obs}$ vs. $1/(OH^-)$ should give a straight line of slope $1/(k_1K+k_2)$ and intercept $K/(k_1K+k_2)$. Such a plot of Kerst's data, and of the rates measured here, do give

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1 A. F. Kerst, Ph.D. Thesis, Harvard University, 1967

2 D. B. Coult, M. Green, J.Chem.Soc., 5478(1964)

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straight lines (Figure 11), from which

k_1K+k_2 = 1.36 x10^{-3} $\underline{M}^{-1}sec^{-1}$, K = 4.6 $\underline{M}^{-1}$, 50°, 50% DME-H_2O

= 3.4 x10^{-3} " = 8.4 $\underline{M}^{-1}$, 40°, H_2O

for the alkaline hydrolysis of Ph(Ph_2PDA).

A similar plot of the data of Coult and Green gives an S-shaped curve, which makes either the data or the explanation suspect in their case. However, considering only the rates at high (OH^-), $k_1K+k_2 \sim 1.7$ x10^{-3} $\underline{M}^{-1}sec^{-1}$, $K \sim 160$ $\underline{M}^{-1}$ for p-NO_2-Ph(Ph_2PDA) in 1:1 i-PrOH-H_2O at 30.5°.

As support for the idea that amide anion forms in alkali, Coult and Green mention that the UV spectrum of p-NO_2-Ph(Ph_2PDA) in alkali "contains a strong peak at 255 nm, which is not present in the reactants or products." Similar behavior is shown by Ph(Ph_2PDA).

The pK of the PDA can thus be determined spectrophotometrically. About 0.4 µl of a 7x10^{-2} $\underline{N}$ solution of Ph(Ph_2PDA) in methanol was added to 2.0 ml 1 $\underline{N}$ $NaClO_4$ in a stoppered UV cell. To both the cell and the 1 $\underline{N}$ $NaClO_4$ blank was added 10 $\underline{N}$ NaOH by syringe, the UV spectrum being recorded after each addition. The original spectrum (λ_{max} 227 nm, OD 0.23; λ_{max} 270 nm, OD 0.02) grew more intense at higher wavelengths (λ_{max} 248; shoulder 280 nm, OD 0.04). Measuring the OD change at 250 nm, correcting for dilution, and plotting as a titration (Figure 12) gives a half-titration point of 20 µl 10 $\underline{N}$ NaOH

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in 2.0 ml. Thus, according to this rough UV titration, K = 10 $\underline{M}^{-1}$ at room temperature, as compared with the kinetically determined K = 8.4 $\underline{M}^{-1}$ at 40°.

UV Titration of Ph(Ph_2PDA)

Volume 10 $\underline{N}$ NaOH	OD^{250}	OD_{corr}	$\frac{(OD_{corr} - 0.011)}{(0.180 - OD_{corr})}$	
0 μl	0.011	0.011	0	
5	0.045	0.045	0.25	
10	0.072	0.072	0.565	(0.1 slidewire)
15	0.079	0.079	0.69	(0-1 slidewire)
20	0.095	0.095	1.01	
30	0.111	0.113	1.52	
40	0.126	0.129	2.31	
200	0.160	0.176	41	
400	0.148	0.178	84	

$$OD_{corr} = OD^{250} \times \frac{2.0+Volume}{2.0}$$

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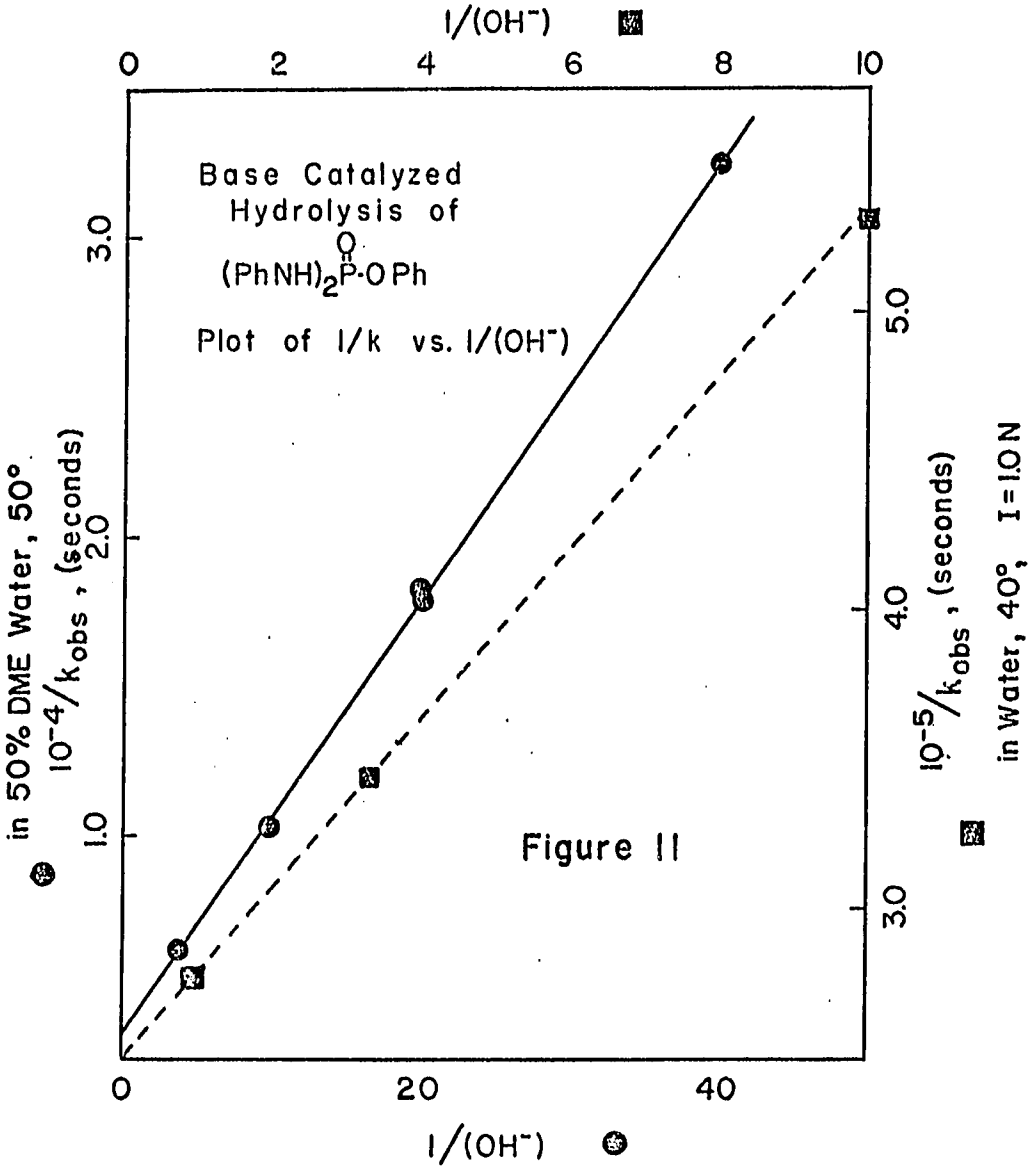

Figure 11

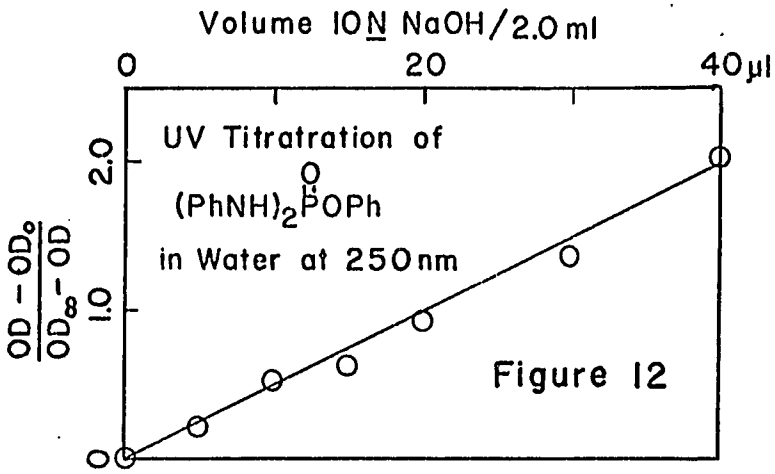

Figure 12

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Phosphoramidate Basicity

An attempt was made to set a limit on the pK for protonation of a phosphoramidate. The o-nitroaniline-perchloric acid/acetic acid-water indicator system of Wiberg and Evans[1] was prepared by R. Kluger.[2]

$H_o = -0.4$
$I = 0.30$ M
$(Ind) = 2.4 \times 10^{-4}$ M

$HClO_4$	HOAc	$NaClO_4$	o-NO_2-aniline
5g 0.82N	95g 99.8%	3.17g	3.4mg

The effect on OD^{400} of adding $Ph(Me_4PDA)$ was compared with the effect of adding 2-methylpiperidine. After extrapolating back to zero time to cancel hydrolysis, it seemed that the PDA was no more than 3% protonated at H_o=-0.4 .

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1 K. Wiberg,R.Evans, J.Am.Chem.Soc., 80, 3019 (1958)
2 R. Kluger, Ph.D. Thesis, Harvard University, 1969

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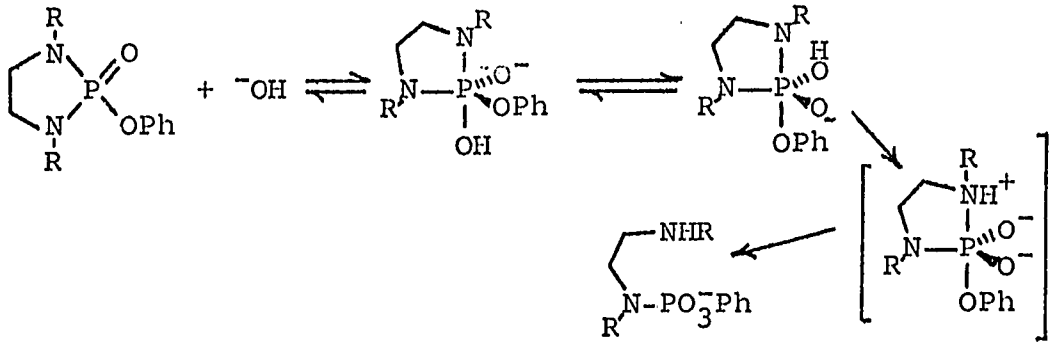
Methanolysis

Various schemes can be proposed to explain the occurence of P-N cleavage in the alkaline hydrolysis of the Ph(alkyl$_2$-enePDA) by invoking proton transfer from the attacking OH^- to the leaving nitrogen. For example,



If such an internal proton transfer is involved in hydrolysis, methanolysis should either not involve P-N cleavage or should be much slower than hydrolysis. In order to make this test, the methanolysis of Ph(Me$_2$enePDA) in $NaOCD_3/CD_3OD$ was studied.

A 1 N $NaOCD_3$ solution was prepared in a nitrogen-filled dry bag by reacting 14 mg sodium metal with ½ ml CD_3OD and diluting to 0.6 ml with CD_3OD. Half of this solution was added to an NMR tube with 10 mg Ph(Me$_2$enePDA) to give a solution 0.15 N in PDA. The NMR tube was capped, removed from the dry bag, and the NMR spectrum of the solution recorded at intervals during the period of a few days.

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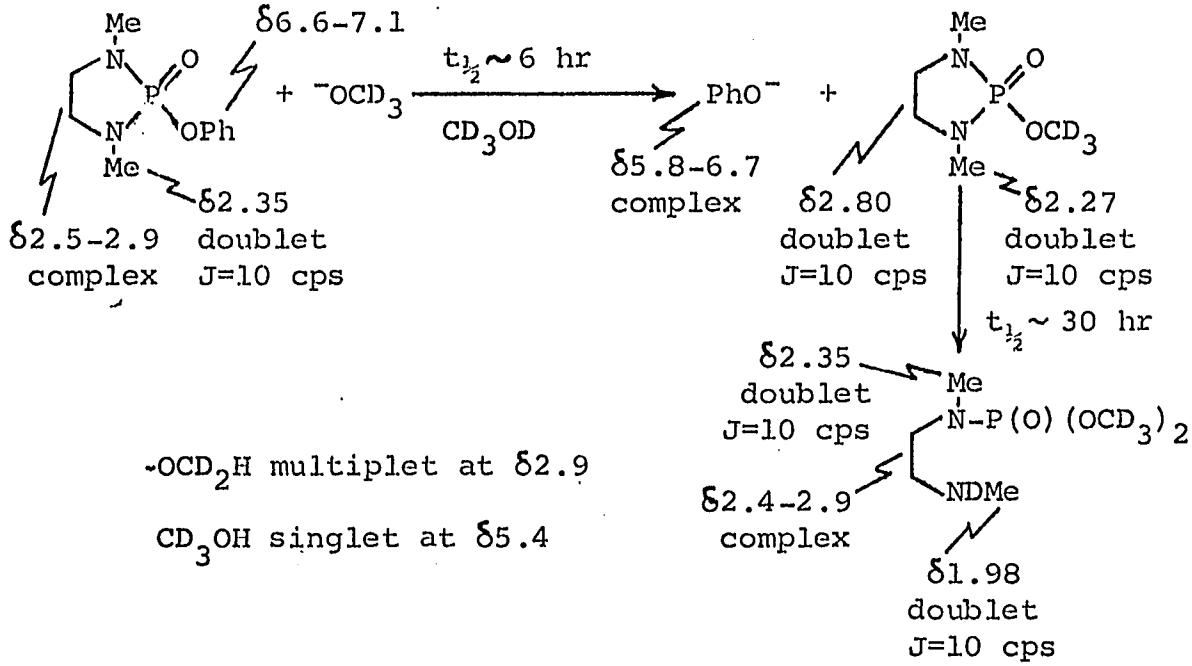
The NMR spectra of the reaction mixture indicate that the predominant path for base-catalyzed methanolysis is loss of phenoxide ion followed by cleavage of one P-N bond.



Aqueous titration to pH 7 with 0.1 N HCl of the used solution after two months showed that it was 0.78 N in base.

A half-time of 30 hours in 0.8-1.0 N $^{-}OCD_3$ at room temperature (21-26°) corresponds to a rate constant for P-N cleavage of $k_{CD_3O^-} = 0.693/(3.6\times10^3 \times 30 \times 0.9\pm0.1) = 0.8 \times10^{-5} M^{-1}$ sec^{-1}, which is about a factor of 5 slower than the rate constant obtained by NMR spectrometry at room temperature for P-N cleavage in $NaOD/D_2O$ of Ph(Me$_2$enePDA) (p 51).

This is reasonably close agreement considering the differences between the two solvents, and indicates that the hydroxyl

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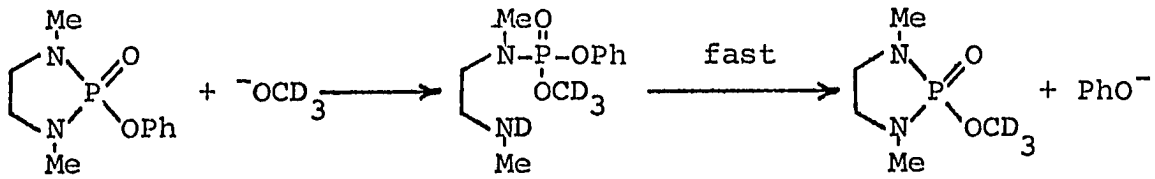
proton is not transfered before the rate determining step during hydrolysis.

This crude experiment leaves open a number of possibilities however. Loss of PhO^- during methanolysis might really be a two-step process involving P-N cleavage and rapid ring reclosure.



This would mean that methanolysis was faster than $0.8 \times 10^{-5} \underline{M}^{-1} sec^{-1}$.

A more serious possibility is that the methanolysis reaction observed was not really base-catalyzed. This was ruled out by dissolving the PDA in CD_3OD without any base. NMR spectra after 400 hours at room temperature showed less than 10% reaction.

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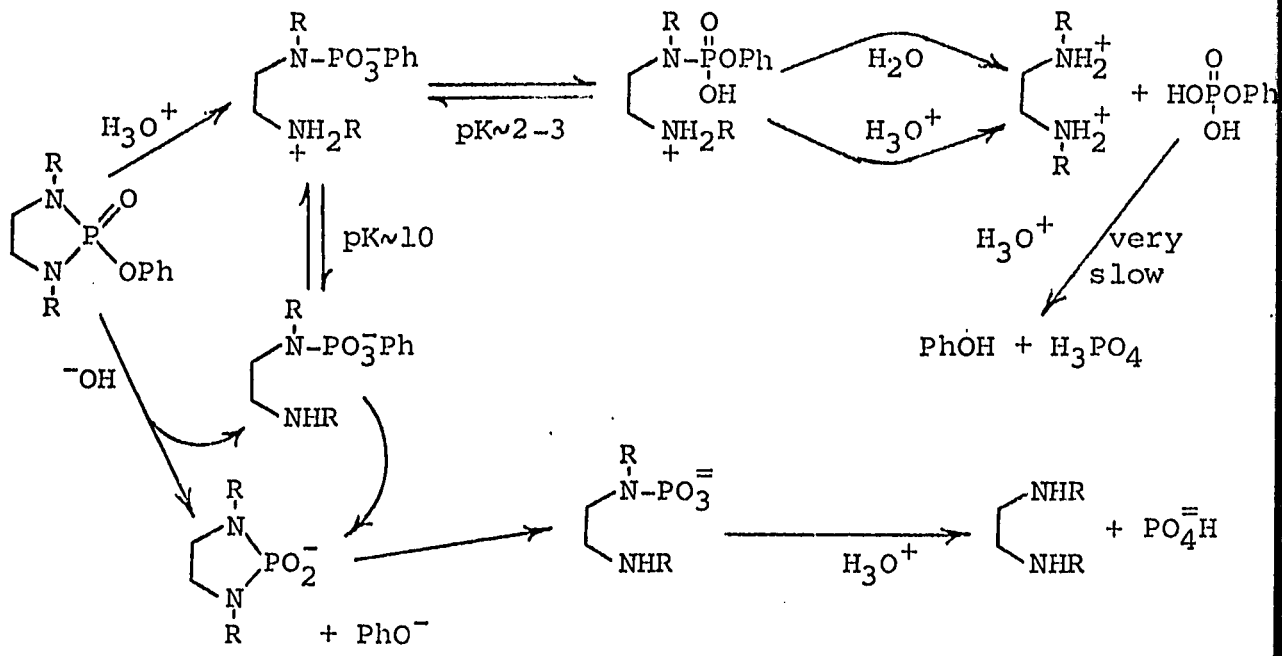
Discussion

The cyclic phosphorodiamidates studied here have three potentially hydrolyzable bonds, and the products of the various hydrolytic cleavages each contain several ionizable amino and phosphoric acid groups. To rationalize most of the results therefore requires a rather complicated scheme of the following sort:



Not all of these steps were or could be observed for any one compound.

Considering the steps in reverse order:

1) $(HO)_2\overset{O}{\overset{\|}{P}}OPh \longrightarrow H_3PO_4 + PhOH$

Barnard et al.[1] found the rate constant for hydrolysis of phenyl phosphate in 0.5-4 N $HClO_4$ to be $4\times10^{-5}sec^{-1}$ at 100°, with an activation energy of 29 kcal/mole, which can be extrapolated to k = $2\times10^{-7}sec^{-1}$ at 55°. This reaction is thus too slow to be of importance except during the very slow hydrolysis of Ph(t-Bu_2enePDA).

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[1] P. W. C. Barnard, et al., J.Chem.Soc. B, 1966, 227

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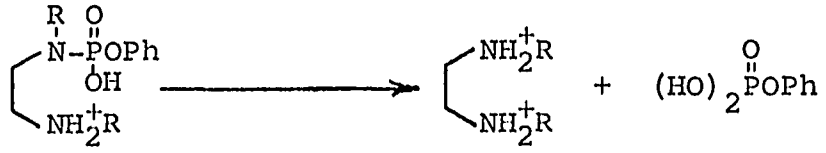
The rate constant for production of phenol from $PhOPO_3H_2$ during the secondary hydrolysis of Ph(t-Bu_2enePDA) in 1 N HCl at 30° was found to be 5 x10^{-7}sec^{-1}, which is reasonably close to the extrapolated value of 2 x10^{-7}sec^{-1}.

2) 

Hydrolysis of the second P-N bond seemed to have a half-time of about 10 minutes in 1 N acid when R=H. At neutral pH's (pH >5), where the phosphoramidate dipolar ion is the major ionic species, the reaction was not detected. These results are compatible with those of Öney and Caplow[1], who found that $H_2NP(O_2^-)OMe$ was stable in water whereas $H_2N\overset{O}{\overset{\|}{P}}(OH)OMe$ hydrolyzed with a water rate of 0.58 hr^{-1} and an acid-catalyzed rate constant of 5.6 M^{-1}hr^{-1} at 37°. These rate constants correspond to a half-time of 7 minutes in 1 N acid.

The effect of the substituent R on the rate of hydrolysis can be estimated on the basis of the work of Garrison and Boozer[2]. They studied the acid-catalyzed hydrolysis of $2,4\text{-}Cl_2\text{-}PhO\overset{O}{\overset{\|}{P}}(OMe)NHR$, R = Me, Et, ..., t-Bu, and they found that bulky R's lowered the rate. In particular, when R=t-Bu the rate was 100 times slower than when R=Me. Applying the

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[1] I. Öney, M. Caplow, J.Am.Chem.Soc., 89, 6972(1967)

[2] A. W. Garrison, C. E. Boozer, J.Am.Chem.Soc., 90, 3486(1968)

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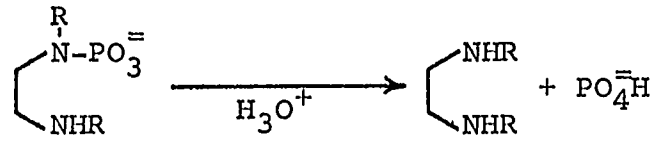
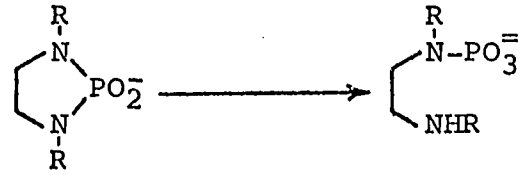
same factor to the present work gives a predicted half-time of 10^3 minutes (16 hr) at 30° in 1 N HCl when R=t-Bu. Such a half-time is nearly equal to that found for the hydrolysis of Ph(t-Bu$_2$enePDA) ($t_{1/2} \sim 20$-40 hr at 30° in 1 N HCl) and may help to explain why such poor first-order kinetic plots were obtained for this compound.

3) 

The phosphoramidate dianion should be hydrolytically stable[1], as it was found to be (see R = H,Me) in strong alkali. However, the fact that the hydrolysis to the diamine occured in several cases when a large excess of base was not present indicates that the reaction is rapid in the presence of acid.

4) 

This reaction was actually observed only when R = Me, but presumably it occurs in all cases. It seems to be rapid when R = H, since the cyclic diamide was not detected even in alkali (see Ph(H$_2$enePDA) Secondary Reactions).

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1 T. Oney, M. Caplow, J.Am.Chem.Soc., 89, 6972(1967)

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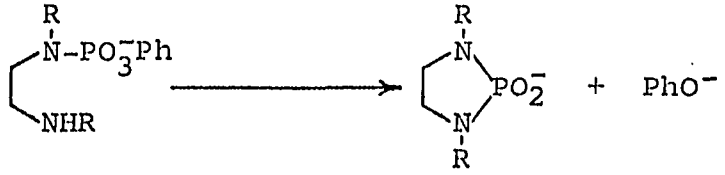
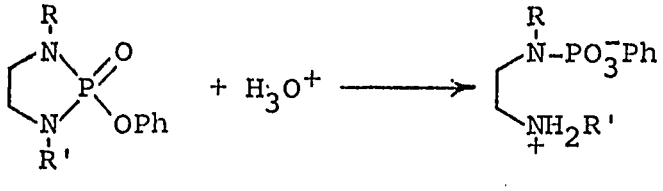
5) 

The production of phenoxide from the ring-opened amidate was observed in several cases. The reaction presumably occurs by nucleophilic attack on phosphorus by the free amino group with expulsion of PhO^-, since when R = Me the cyclic diamide was detected by NMR spectroscopy, and since for R = H the rate of reaction was independent of pH at pH's above the pK of the amino group.

Rate of Ring Reclosure of $RNHCH_2CH_2NRPO_3^-Ph$

R	k	temp.	Solution
H	1.8×10^{-4}	80°	2 N NaOD
H	3.0×10^{-6} sec^{-1}	40°	1 N NaOH
Me	9×10^{-6}	80	2 N NaOD
Et	2.5×10^{-6}	80	1 N KOH
i-Pr	1.0×10^{-6}	87	1 N NaOH

6) 

In general, the acid-catalyzed hydrolysis of the enePDA's seemed to have a small activation energy ($\Delta H^{\ddagger}$ = 5-10 kcal/mole), a solvent isotope effect $k_{D_3O^+}/k_{H_3O^+}$ of about 2, a slower rate in mixed solvents, and an extreme sensitivity to the size of the substituent R. Buffer catalysis was generally undetectable.

These results indicate that the acid-catalyzed hydrolysis

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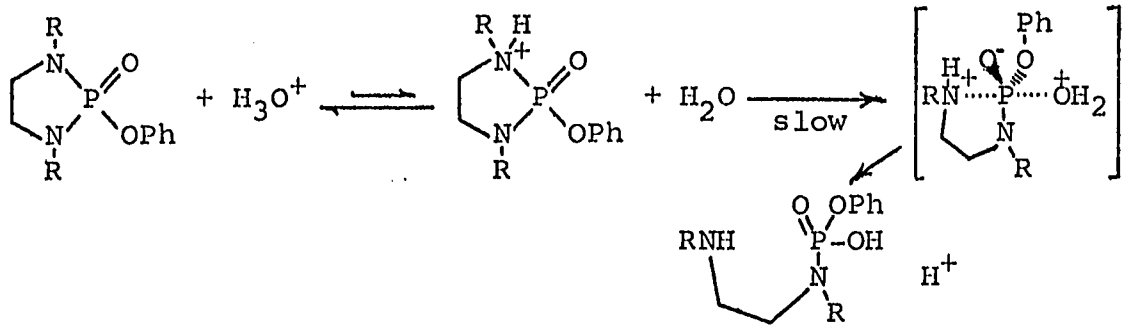
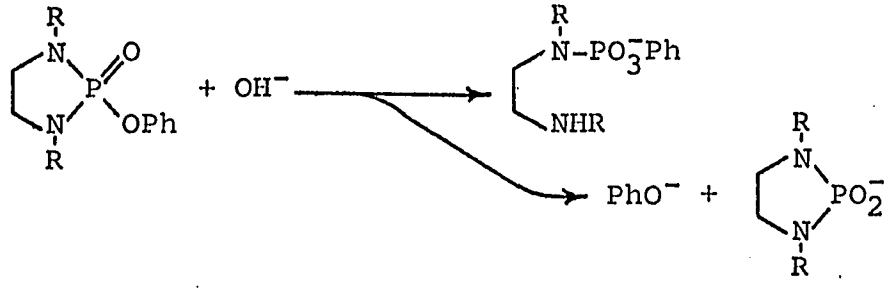
proceeds by attack of water on the N-protonated PDA.



The solvent isotope effect indicates pre-rate-determining step protonation, while the large steric effect is difficult to explain if attack by water occurs after the transition state.

7)



The base-catalyzed hydrolysis of the enePDA's provides the only surprising results; namely, P-N cleavage in alkali in preference to P-OPh cleavage. The reaction seemed to have an activation energy on the order of 15-18 kcal/mole, and a small solvent isotope effect ($k_{OD^-}/k_{OH^-} \sim 1.2$ when R=H, $k_{OD^-}/k_{OH^-} \sim 1.0 \pm 0.05$ when R=Me). The effect of substituents on the rate was in the same direction as, but even larger than, their effect on the rate of the acid-catalyzed reaction. The fraction of exocyclic cleavage (PhO^- production) was not greatly influenced by temperature or ionic strength, and was on the order

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of 10% for R = H, Me, Et; 35% for R = i-Pr; and perhaps 100% for R = Ph. Buffer catalysis was generally small, but detectable for R = H. Whether the catalysis was nucleophilic or general base was not determined.

A collection of the various rate constants determined during this work along with some pertinent rates from the work of others is given in Table 1.

In this table it can be seen that, in both acid and base, the cyclic compounds hydrolyze many orders of magnitude faster than do their acyclic analogues. Also, the phosphoramidates of aliphatic amines hydrolyze orders of magnitude faster in acid than do the corresponding amides of aryl amines. The large N-H/N-Me rate difference in alkali which, as mentioned in the introduction, might be due to a difference in mechanism, appears again. However, the table of rates also illustrates what appear to be sizeable steric decelerations for hydrolysis in both acid and base.

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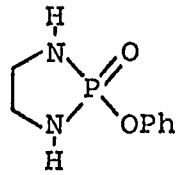
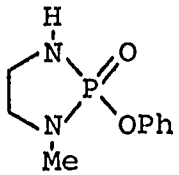
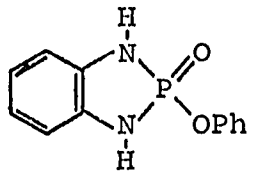
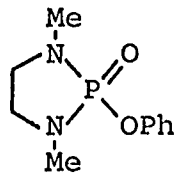
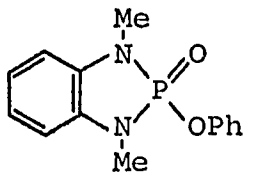
Table 1

Rate Constants for Hydrolysis

Compound	k_{H^+} ($M^{-1}sec^{-1}$)	k_{OH^-} ($M^{-1}sec^{-1}$)
	3.4×10^5 (30°) $k_D/k_H = 2.2$ $\Delta H^{\ddagger} = 5 \pm 4$ kcal/M 0.5×10^5 (25°, 33% THF)	4.2 (30°) $k_{OD}/k_{OH} = 1.3$ $\Delta H^{\ddagger} = 17 \pm 4$ kcal/M 91% P-N cleavage
	1.4×10^5 (30°) $k_D/k_H = 2.1$ $\Delta H^{\ddagger} = 6.5 \pm 4$ kcal/M	2.5 (30°) $k_{OD}/k_{OH} = 1.1$ $\Delta H^{\ddagger} = 17 \pm 4$ kcal/M 94% P-N cleavage
	1.1 (30°) 1.6 (30°, 50% DME) a)	$(1.2 \pm 0.3) \times 10^3$ (30°) 1.0×10^2 (30°, 50%DME) a) $\Delta H^{\ddagger} = 12 \pm 1$ kcal/M
	1.3×10^2 (30°) $\Delta H^{\ddagger} = 6.5 \pm 2$ kcal/M	1.2×10^{-4} (30°) $k_{OD}/k_{OH} = 1.0 \pm 0.05$ $\Delta H^{\ddagger} = 15 \pm 2$ kcal/M 95% P-N cleavage
	1.3×10^{-4} (30°, 50% DME) a)	2.9×10^{-2} (30°, 50%DME) a) $k_{OD}/k_{OH} = 1.0$ $\Delta H^{\ddagger} = 13 \pm 0.5$ kcal/M

a) A. F. Kerst, Ph.D. Thesis, Harvard University, 1967

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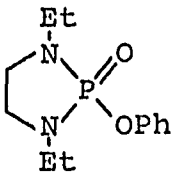
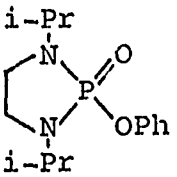
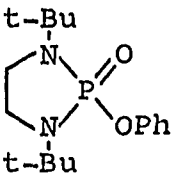
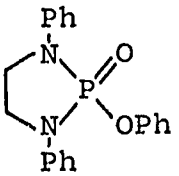
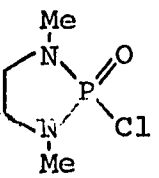
Compound	k_{H^+} ($M^{-1}sec^{-1}$)	k_{OH^-} ($M^{-1}sec^{-1}$)
	30 (30°) $\Delta H^{\ddagger}$ = 5±5 kcal/M	2×10^{-6} (30°) 1.4×10^{-4} (69°) 94% P-N cleavage
	0.4 (30°) $\Delta H^{\ddagger}$ = 6±1 kcal/M	5.5×10^{-6} (87°) 65% P-N cleavage
	10^{-5} (30°)	$< 1.3 \times 10^{-9}$ (110°)
	6×10^{-4} (40°)	10^{-4} (61°, 50% MeOH) 5×10^{-4} (80°, 20% MeOH) < 25% P-N cleavage
	1×10^{4} (29°)	$k_{H_2O} = 7.2 \times 10^{-3} sec^{-1}$ (29°)
$(Me_2N)_2\overset{O}{\overset{\|}{P}}-Cl$		$k_{H_2O} = 1.9 \times 10^{-3} sec^{-1}$ (10°) b)

b) P. S. Traylor, F. H. Westheimer, J.Am.Chem.Soc., 87, 553(1965)

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Compound	k_{H^+} ($M^{-1}sec^{-1}$)	k_{OH^-} ($M^{-1}sec^{-1}$)
$(MeNH)_2\overset{O}{\overset{\|}{P}}-OPh$	1.2×10^{-3} a) (25°, 80% CD_3OD)	2.5×10^{-3} (30°, 50%DME) a) $\Delta H^{\ddagger} = 16 \pm 1$ kcal/M
$(Me_2N)_2\overset{O}{\overset{\|}{P}}-OPh$	8.8×10^{-5} a) (25°, 80% CD_3OD)	3×10^{-6} (91°, 50%DME) a) $\Delta H^{\ddagger} = 15 \pm 2$ kcal/M
$(PhNH)_2\overset{O}{\overset{\|}{P}}-OPh$	7.5×10^{-5} a) (75°, 78%DMSO-d_6)	3.4×10^{-3} (40°) 1.4×10^{-3} (50°, 50%DME) a) $\Delta H^{\ddagger} = 17 \pm 1$ kcal/M
$(PhNMe)_2\overset{O}{\overset{\|}{P}}-OPh$	7.5×10^{-4} a) (75°, 78%DMSO-d_6)	4×10^{-6} (91°, 50%DME) a)
$H_2N-\overset{O}{\overset{\|}{P}}(OMe)_2$	1.5×10^{-3} (37°) c)	8.3×10^{-2} (37°) c)
$Me_2N-\overset{O}{\overset{\|}{P}}(OMe)_2$	6.7×10^{-2} (28°) d) $\Delta H^{\ddagger} = 10$ kcal/M	2.3×10^{-4} (100°) c)
$(Me_2N)_3PO$	3.7×10^{-6} (25°) e)	$< 10^{-5}$ (100°) e)

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c) I. Öney, M. Caplow, J.Am.Chem.Soc., 89, 6972(1967)

d) M. Selim, T. N. Thanh, Compt.rend., 250, 2724(1960)

e) D. F. Heath, P. Casapieri, Trans.Far.Soc., 47, 1093(1951)

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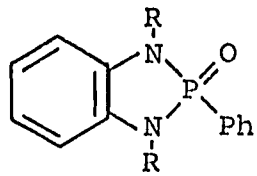
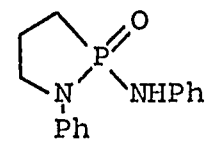
The fact that P-N cleavage is the dominant path for the alkaline hydrolysis of the Ph(alkyl$_2$enePDA)'s should not have been a total surprise. P-N cleavage in base is known, and may even be rapid when a five-member ring is involved. Dannley and Grava [1] found that o-phenylenediamine phenylphosphonodiamide (I a) reacts exothermically with 1 N NaOH to open the ring, and that the N,N'-dimethyl derivative (Ib) has a half-life of about 2 minutes in boiling 1 N NaOH. Similarly, Helferich and Curtius [2] state that N-phenylphostamanilide (II) dissolves with decomposition in dilute warm alkali, although the corresponding six-member ring compound is fairly stable to alkali.



I a) R = H
b) R = Me



II

These previous results provide other examples of both P-N cleavage in base and a large N-H/N-Me rate difference, but certain facts still need explanation. First, the large rate difference between the N-H and N-Me compounds, which we set out to explain in the first place, must be rationalized. Second, phenoxide ion is a much better leaving group than

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1 R. L. Dannley, A. Grava, Can.J.Chem., 43, 3377(1965)

2 B. Helferich, U. Curtius, Annalen, 655, 59(1962)

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amine anion is, yet the Ph(alkyl$_2$enePDA)'s cleave predominantly at the P-N bond in base. Third, aniline anion should be a better leaving group than alkyl amine anion, yet the N-aryl PDA's cleave mainly at the P-OPh bond in base.

Considering the N-H/N-Me rate difference first, it seems that, at least for the cyclic amides, this difference can be explained on the basis of steric hindrance without invoking a change in mechanism. The main reason for deciding this is the similar effect of substituents on the rates of hydrolysis in both acid and base. The rate constants for hydrolysis of Ph(alkyl$_2$enePDA) fall in the order H > Me > Et > i-Pr > t-Bu, which is the same order as the increasing steric bulk and electron-donating power of the substituents (as measured by Taft's σ^* and E_s [1]).

An attempt to make this argument more quantitative by fitting the rates to a linear-free-energy equation is hampered by the sparcity of the data and the multiplicity of available substituent parameters. However, following the lead of Garrison and Boozer[2] we can try the equation

$$\log(k/k_o) = \rho^* \sigma^* + \delta E_s$$

k = rate of reaction
k_o = k for R = Me
σ^* = Taft's polar substituent constant
E_s = Taft's steric substituent constant

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1 R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, London, 1956

2 A. W. Garrison, C. E. Boozer, J.Am.Chem.Soc., 90, 3486(1968)

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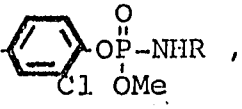
Garrison and Boozer correlated the rate constants for acid-catalyzed hydrolysis of a series of N-substituted phosphoramidates,  , using this equation and found $\rho^* = +3.6$, $\delta = +0.6$.

Attempting to treat the cyclic PDA's in the same manner,

Linear Free Energy Equation:
Fitting the Ph(R,one)PDA) Hydrolysis Rates

$4E_s+4\sigma^*$	$\log\left\{\frac{k_{H^+}^{30^\circ}}{k_o}\right\}$	R (σ^*, E_s)	$\log\left\{\frac{k_{OH^-}^{30^\circ}}{k_o''}\right\}$	$5E_s+5.5\sigma^*$
+6.92	+3.42	H (+0.49, +1.24)	+4.54	+8.90
0	0	Me (0, 0)	0	0
-0.68	-0.63	Et (-0.1, -0.07)	-1.8	-0.90
-2.64	-2.7	i-Pr (-0.19, -0.47)	-3.2 (a)	-3.40
-7.36	-7.1	t-Bu (-0.30, -1.54)	<-7.6 (b)	-9.35
-1.2	-5.7 (d)	Ph (+0.6,-0.9)	-1.1 (c)	-1.20

rate constants at 30° extrapolated from
a) $k = 5.5\times10^{-6}\underline{M}^{-1}sec^{-1}$ at 87°
b) $k = 10^{-9}\underline{M}^{-1}sec^{-1}$ at 110°
c) $k = 5\times10^{-4}\underline{M}^{-1}sec^{-1}$ at 80°
using $\Delta H^{\ddagger}$ = 16 kcal/mole
and from d) $k = 6\times10^{-4}\underline{M}^{-1}sec^{-1}$ at 40° using $\Delta H^{\ddagger}$ = 6 kcal/M

$k_o = k_{H^+}^{30^\circ}$ when R=Me, $= 1.3\times10^{2}\underline{M}^{-1}sec^{-1}$
$k_o'' = k_{OH^-}^{30^\circ}$ when R=Me, $= 1.2\times10^{-4}\underline{M}^{-1}sec^{-1}$

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The fit of the rates to the linear free energy relation is not good considering we have two parameters to fit only five points. The fact that the calculated $\log(k/k_o)$ for R=H is much too large in both acid and base is quite probably due to too large a value of E_s. A value of E_s=0.36 for R=H would fit the results in both acid and base, but adding another variable parameter like that couldn't make the fit worse. The value of E_s does depend strongly and irregularly on the relative positions of substituent and reaction site, however, so it is difficult to decide which set of values of E_s to use for this relatively rigid system. The other major discrepancy in the calculated $\log(k/k_o)$, the 4.5 power of ten difference in calculated and observed k/k_o for R = Ph in acid, is presumably due to inhibition of protonation of the amide nitrogen because of N-Ph resonance.

However, assuming that the results have at least approximate validity, we can see several things. The ρ^* for acid-catalyzed hydrolysis is essentially the same as that found by Garrison and Boozer, indicating that the polar effect for acid-catalyzed reaction operates mainly on the leaving-group nitrogen. Both ρ^* and δ are quite large, suggesting that the reactions are very sensitive to both polar and steric effects. This is not hard to understand with respect to the steric

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inhibition, but the fact that the polar effects also work in the same direction in both acid and base is rather puzzling.

In any case, it seems that it is unnecessary to invoke the metaphosphoramide path in order to explain the large N-H/N-Me rate difference in base for the cyclic amidates. The original basis for this work, that the metaphosphoramidate path would not operate for the cyclic compounds, thus seems to be the case. This may be because it is unfavorable to put a double bond in a five-member ring with phosphorus, as originally thought; or more likely, it may be because the presence of a five-member ring accelerates nucleophilic attack so much that attack by OH^- becomes faster than the unaccelerated rate for the abstraction/elimination path.

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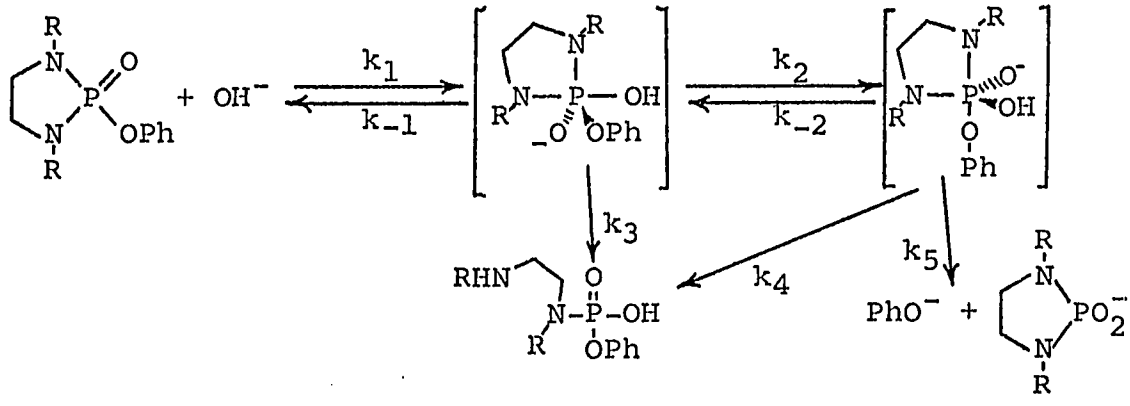
Granting that all the enePDA's hydrolyze in alkali by the same mechanism, what are the details of that mechanism ? The enhanced rates of hydrolysis for the cyclic PDA's over those of their acyclic analogues, the steric deceleration effect, and the formation of products of both endocyclic and exocyclic cleavage all indicate that hydrolysis proceeds by nucleophilic attack on phosphorus by hydroxide ion to give a pentacovalent intermediate, which may pseudoratate before breaking down to products.



This seems to be the usual path for the alkaline hydrolysis of cyclic phosphorus compounds[1].

The problem of P-N cleavage is still not explained, though. Since we expect PhO^- to leave much faster than the ring cleaves ($k_5 \gg k_3, k_4$), the problem resolves to one of comparing the relative rates of pseudorotation (k_2) and P-N cleavage (k_3).

---

1 F. H. Westheimer, Accounts of Chemical Research, 1, 70 (1968)

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The extreme basisity of amine anion, plus the fact that the N-alkyl but not the N-aryl cyclic PDA's cleave at the P-N bond, suggests that the leaving-group nitrogen is protonated before or as it leaves. A more careful determination of the % exocyclic cleavage in both H_2O and D_2O might allow some decision to be made on this point:

$$\frac{(\%\ PhO^-\ in\ H_2O)}{(\%\ PhO^-\ in\ D_2O)} = \frac{k_2^H/(k_3^H + k_2^H)}{k_2^D/(k_3^D + k_2^D)} \approx \frac{k_3^D}{k_3^H} \qquad \text{if } k_3 > k_2,\ k_2^H = k_2^D$$

$\gtrsim 1$ if protonation preceeds P-N cleavage

< 1 if protonation coincides with P-N cleavage

In the few cases (Ph(MeHenePDA) and Ph(Me_2enePDA)) for which this ratio was determined, it was less than 1, but not by much more than experimental error.

On the basis of Muetterties' preference rule[1,2] that the more electronegative substituent prefers to occupy the apical (entering-leaving) positions in the pentacovalent species, we can explain the fact that Kerst's PhenePDA's hydrolyze in base about 10^2x faster than do the corresponding enePDA's. The more electronegative N-aryl group is more readily placed in an apical position than is the N-alkyl group, therefore the intermediate is formed more rapidly and the hydrolysis is more rapid. On the basis of the available evidence, however,

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[2] E. L. Muetterties, W. Mahler, R. Schmutzler, Inorg.Chem. 2, 613(1963)

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it is impossible to decide whether the N-aryl intermediates also pseudorotate more rapidly than do the N-alkyl intermediates, or whether the difference in nitrogen basicity is enough to explain the fact that the N-aryl compounds cleave solely exocyclically.

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Extensions

There are a number of problems related to this work which might be investigated. Many of these have to do with amino-phosphoranes (pentacovalent phosphorus species containing at least one P-N bond), specifically, their stability, pseudo-rotation, and mode of breakdown. Aside from investigating the phosphoranes directly in inert solvents, it might be helpful to try to determine the mechanism of P-N cleavage in base by looking at the solvent isotope effect and buffer catalysis for one of the cyclic phosphonamides (e.g. I or II, p 84) or even for one of the acyclic amides (e.g. $PhP(O)(NH_2)_2$[1]).

Since the substituent effects for the cyclic phosphorus compounds are so large, they should provide an excellent testing ground for semi-empirical structure-rate correlations such as Taft's σ^* and E_s[2]. Comparison with the acyclic compounds will probably require some sort of conformational analysis such as the method used by Lifson[3]. Such an undertaking would be a major project, however.

With respect to the metaphosphoramide path, the cyclic

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1 W. C. Smith, L. F. Audrieth, J.Org.Chem., 22, 265(1957)

2 R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, ed., John Wiley and Sons, London, 1956

3 M. Bixon, S. Lifson, Tetrahedron, 23, 769(1967)

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compounds seem to provide no information other than that a large N-H/N-Me rate difference is no proof of a change in mechanism. The measurable pK for the amide proton of the $X\overset{O}{\overset{\|}{P}}(NHPh)_2$ is promising, however. If the results for X = PhO and X = p-NO_2-PhO are correct, the effect of X on the rate constant for hydrolysis (k_1K+k_2) is small but the effect on the pK is very large. This bears looking into.

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Appendices

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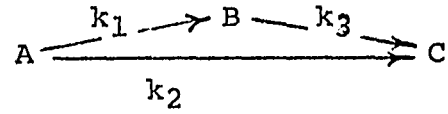
Appendix I

Computer Least-Squares Fit

For a scheme of the sort



the integrated kinetic equations are

$$A = A_o\, e^{-(k_1+k_2)t} \qquad C = A_o - A - B$$

a) for $k_1+k_2 \neq k_3$ $\qquad B = \frac{k_1 A_o}{k_1+k_2-k_3}\left\{e^{-k_3 t} - e^{-(k_1+k_2)t}\right\}$

b) for $k_1+k_2 = k_3$ $\qquad B = k_1 A_o t\, e^{-k_3 t}$

In the case under consideration, Ph(i-Pr$_2$enePDA) + OH^-, we are measuring C, phenoxide, so we want to fit the data to an expression of the form (ignoring case b)

$$C_t = X_1\, e^{-X_2 t} - X_3\, e^{-X_4 t} + X_3 - X_1$$

where $\quad X_1 = (k_3-k_2)\, A_o \,/\, (k_1+k_2-k_3)$

$$X_2 = k_1 + k_2 \qquad X_4 = k_3$$

$$X_3 = k_1\, A_o \,/\, (k_1+k_2-k_3)$$

In particular, for a least-squares fit, we want to minimize the sum of the squares of the errors

$$F = \sum (C_{t_i} - C_i)^2$$

C_{t_i} = calculated value at time t_i
C_i = actual value at time t_i

with respect to the X_j .

That is, we want $\partial F/\partial X_j = 0$ for j=1,2,3,4.

Although we could probably solve these four equations in four unknowns by iterating each unknown separately, a quicker method suggests itself. We know that for small changes in the X_j

$$\Delta\, \partial F/\partial X_j \simeq \sum_{k=1}^{4} \left\{\partial^2 F/\partial X_j \partial X_k\right\}\, dX_k$$

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Since, given X, we can calculate all of these partial derivatives:

$$\partial F/\partial x_j = 2 \sum_i (c_{t_i} - c_i) \cdot \partial c/\partial x_j$$

$$\partial^2 F/\partial x_j \partial x_k = 2 \sum_i \{(c_{t_i} - c_i) \cdot \partial^2 c/\partial x_j \partial x_k + (\partial c/\partial x_j)(\partial c/\partial x_k)\}$$

$$\partial c/\partial x_1 = e^{-x_2 t} - 1$$

$$\partial c/\partial x_2 = -x_1 t\, e^{-x_2 t}$$ and so on; we now have four linear equations in four unknowns:

$$a_{11}y_1 + a_{12}y_2 + a_{13}y_3 + a_{14}y_4 = a_{15}$$
$$a_{21}y_1 + a_{22}y_2 + a_{23}y_3 + a_{24}y_4 = a_{25}$$
$$a_{31}y_1 + a_{32}y_2 + a_{33}y_3 + a_{34}y_4 = a_{35}$$
$$a_{41}y_1 + a_{42}y_2 + a_{43}y_3 + a_{44}y_4 = a_{45}$$

$$a_{ij} = \frac{\partial^2 F}{\partial x_i \partial x_j} \qquad i,j = 1,2,3,4$$

$$a_{i5} = -\frac{\partial F}{\partial x_i}, \quad y_i = dx_i$$

Since we are changing the x_j cooperatively, the iteration should converge much more rapidly than when we iterate the x_j separately.

For a simple first-order reaction, $A \xrightarrow{k_1} B$, the most general form for the change in any extensive property as a function of time is $c_t = x_1\, e^{-x_2 t} - x_1 + x_3$. The least-squares analysis of this three-parameter equation is similar to, though much shorter than, the analysis given above for a four-parameter equation. The computer program is correspondingly similar.

The Fortran programs and the results from the IBM 1620 are given on the following pages.

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```
C                    LEAST SQUARES FIT
C                OF KINETIC DATA TO THE SCHEME
C         C = X1 * EXP(-X2*TIME) - X3 * EXP(-X4*TIME) + X3 - X1
C
ZZFORX
      DIMENSION DX(5,4),X(4),DELT(4),CON(13),TIM(13)
      COMMON DX
C               INPUT DATA
      READ 90,NN,(TIM(I),CON(I),I=1,NN)
   90 FORMAT(I2/(2F6.3))
C               INPUT STARTING GUESSTIMATES
  170 ACCEPT 180,X(1),X(2),X(3),X(4)
  180 FORMAT(4E10.7)
      ACCEPT 401,RED
  401 FORMAT(F3.1)
C               SET INITIAL VALUES TO ZERO BEFORE SUMMING
  185 FUNC=0.
      DO 190 I=1,5
      DO 190 J=1,4
  190 DX(I,J)=0.
C               CALCULATE DERIVATIVES
      DO 200 I=1,13
      EX1=EXPF(X(2)*TIM(I))
      EX2=EXPF(X(4)*TIM(I))
      TM1=(1.0/EX1-1.0)
      TM2=1.0/EX2-1.0
      CT=X(1)/EX1-X(3)/EX2+X(3)-X(1)
      CDIF=CT-CON(I)
      CTD=CDIF*TIM(I)
      DX(5,1)=DX(5,1)+CDIF*TM1
      DX(5,2)=DX(5,2)-CTD*X(1)/EX1
      DX(5,3)=DX(5,3)-CDIF*TM2
      DX(5,4)=DX(5,4)+CTD*X(3)/EX2
      DX(1,1)=DX(1,1)+TM1*TM1
      DX(3,3)=DX(3,3)+TM2*TM2
      DX(3,1)=DX(3,1)-TM1*TM2
      TM1=TM1*TIM(I)
      TM2=TM2*TIM(I)
      DX(2,1)=DX(2,1)-CTD/EX1-X(1)*TM1/EX1
      DX(4,1)=DX(4,1)+X(3)*TM1/EX2
      DX(3,2)=DX(3,2)+X(1)*TM2/EX1
      DX(4,2)=DX(4,2)-X(1)*X(3)*TIM(I)*TIM(I)/(EX1*EX2)
      DX(4,3)=DX(4,3)+CTD/EX2-X(3)*TM2/EX2
      DX(2,2)=DX(2,2)+CTD*X(1)*TIM(I)/EX1+(X(1)*TIM(I)/EX1)**2
      DX(4,4)=DX(4,4)+CTD*X(3)*TIM(I)/EX2+(X(3)*TIM(I)/EX2)**2
      IF(SENSE SWITCH 4) 130,200
  130 CON(I)=CT
  200 FUNC=FUNC+CDIF*CDIF
      DO 201 I=1,3
      IN=I+1
      DO 201 J=IN,4
  201 DX(I,J)=DX(J,I)
C               OUTPUT RESULTS
      PRINT 300,FUNC
  300 FORMAT(9H     FUNC=,E15.7)
```

NN = number of data points
TIM = time
CON = OD measured
X = parameters to be determined

RED = reduction factor between 0 and 1, to avoid overshoot during iteration

$DX(I,J) = \partial^2 F/\partial X_I \partial X_J$ $I,J=1,2,3,$

$DX(5,J) = \partial F/\partial X_J$

CT = C_{t_i} = calculated OD at time t_i

CDIF = error, observed − calculated

FUNC = F = sum of squares of errors

Print out F

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```
      PUNCH 310,FUNC,X
  310 FORMAT(/9H     FUNC=,E15.7/7H     XI=,4E15.7)
C                CALCULATE CORRECTIONS
   20 DEN=DET (1,2,3,4)
   21 DELT(1)=DET (5,2,3,4)
   23 DELT(2)=DET (1,5,3,4)
   25 DELT(3)=DET (1,2,5,4)
   27 DELT(4)=DET (1,2,3,5)
      DO 40 I=1,4
   40 X(I)=X(I)-DELT(I)*RED/DEN
      IF(SENSE SWITCH 4) 307,314
  314 IF (SENSE SWITCH 1) 315,185
  315 PUNCH 316
  316 FORMAT(51HI DXI1              DXI2              DXI3              DXI4)
  307 PUNCH 308,(TIM(I),CON(I) ,I=1,NN)
  308 FORMAT((F22.2,F8.4))
      DO 301 I=1,5
      IN=6-I
      IF(I-1)290,290,295
  290 INN=4
      GO TO 301
  295 INN=IN
  301 PUNCH 302,IN,(DX(IN,J),J=1,INN)
  302 FORMAT(I1,4E15.7)
   28 PUNCH 30,DEN,DELT
   30 FORMAT(8H  DENOM=,E15.7/7H DELTA=,4E15.7)
C                RECYCLE
      GO TO 185
      END
C
C                      FUNCTION SUBPROGRAM
C            TO CALCULATE THE DETERMINANT OF A 4X4 MATRIX
C                 CHOSEN FROM A 5X4 MATRIX
      FUNCTION DET(J,K,L,M)
      DIMENSION D(5,4)
      COMMON D
      DET=0.
      DO 100 NN=1,3
      IMP=K
      K=L
      L=M
      M=IMP
  100 DET=DET+(D(J,1)*D(K,2)-D(K,1)*D(J,2))*(D(L,3)*D(M,4)-D(M,3)*D(L,4)
     2)+(D(J,3)*D(K,4)-D(K,3)*D(J,4))*(D(L,1)*D(M,2)-D(M,1)*D(L,2))
   53 RETURN
```

Solve the four linear equations by determinants.

Correct the X

Sense Switch 4 is turned on when the iteration has converged. The calculated OD's are then stored during the next iteration, and printed out before stopping.

The program is stopped manually when F seems to have reached a minimum.

```
C                      RESULTS   1.0 N KOH
     FUNC=  7.6272225E-04
     XI= -2.5210000E-01  1.9992000E-02  1.1469000E+00  3.7784000E-03

     FUNC=  7.6271999E-04
     XI= -2.5210168E-01  1.9991853E-02  1.1469034E+00  3.7784063E-03

     FUNC=  7.6272268E-04
```

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```
     XI= -2.5210253E-01  1.9991773E-02  1.1469061E+00  3.7784120E-03
 I DXI1            DXI2            DXI3            DXI4
 5  6.8853000E-05 -5.9825277E-05 -5.0546000E-05 -5.6270000E-03
 4 -7.9160566E+02  1.1485667E+03  5.0778248E+02  7.1635804E+04
 3 -6.4321625E+00  4.6404220E+00  4.8951712E+00
 2 -1.3397390E+01  6.8832927E+01
 1  9.4920801E+00
   DENOM=  5.9873000E+04
  DELTA=  1.2447000E-01  1.1214000E-02 -3.8339000E-01 -7.8975000E-04

     FUNC=  7.6272426E-04
     XI= -2.5210315E-01  1.9991717E-02  1.1469080E+00  3.7784159E-03
 C                  TIME  OD CALC     OBS
                    2.70   .0248      0.033
                   18.30   .1538      0.164
                   41.60   .3091      0.309
                   66.10   .4383      0.432
                   93.00   .5526      0.550
                  139.80   .7073      0.707
                  190.75   .8355      0.833
                  262.75   .9727      0.986
                  378.70  1.1246      1.121
                  488.75  1.2180      1.222
                  616.00  1.2871      1.275
                  717.80  1.3228      1.316
                  882.60  1.3581      1.370
 I DXI1            DXI2            DXI3            DXI4
 5  4.8763000E-05 -4.2724446E-05 -3.5781000E-05 -3.9838500E-03
   DENOM=  5.9880000E+04
  DELTA=  6.4546000E-02  5.7370000E-03 -2.9212800E-01 -6.3817000E-04

 C                   RESULTS   0.2 N KOH
     FUNC=  1.2648381E-03
     XI=  1.4830000E+01  3.9450000E-03  1.6280000E+01  3.7360000E-03

     FUNC=  1.2626306E-03
     XI=  1.4833600E+01  3.9432667E-03  1.6284133E+01  3.7344000E-03

     FUNC=  1.2622182E-03
     XI=  1.4839066E+01  3.9418467E-03  1.6289866E+01  3.7332000E-03
 I DXI1            DXI2            DXI3            DXI4
 5  8.0676340E-03  8.2685870E+00 -7.9402570E-03 -1.0845487E+01
 4 -7.4916942E+03 -1.2689730E+07  7.3068883E+03  1.4827247E+07
 3 -4.9445616E+00 -6.1110291E+03  4.8548724E+00
 2  6.2692136E+03  1.0864239E+07
 1  5.0365370E+00
   DENOM=  1.0000000E+07
  DELTA= -7.0000000E+05  2.1700000E+02 -7.4000000E+05  2.0000000E+02

     FUNC=  1.2683388E-03
     XI=  1.4853066E+01  3.9375067E-03  1.6304666E+01  3.7292000E-03
 C                  TIME  OD CALC     OBS
                    2.70   .0062      0.009
                   18.30   .0429      0.055
                   41.60   .0988      0.100
```

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```
                 66.10    .1583      0.163
                 93.00    .2239      0.222
                139.80    .3366      0.334
                190.75    .4548      0.449
                262.75    .6097      0.600
                378.70    .8235      0.832
                488.75    .9846      0.988
                616.00   1.1258      1.150
                717.80   1.2098      1.212
                882.60   1.3048      1.288
I DXI1           DXI2            DXI3            DXI4
5  8.1600700E-03  9.2061670E+00 -8.0197110E-03 -1.1898577E+01
  DENOM=  1.0000000E+07
 DELTA= -5.2000000E+05  2.8300000E+02 -5.9000000E+05  2.4100000E+02
```

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```
C                    LEAST SQUARES FIT
C                OF KINETIC DATA TO THE SCHEME
C                          A ---k1---> B
C
ZZFORX
      DIMENSION DX(4,3),X(3),DELT(3),CON(15),TIM(15)
      COMMON DX
      READ 90,NN,(TIM(I),CON(I),I=1,NN)
   90 FORMAT(I2/(2F6.3))
      ACCEPT 100,X(1),X(2),X(3),RED
  100 FORMAT(3E10.7,F3.1)
  115 FUNC=0.
      DO 120 I=1,4
      DO 120 J=1,3
  120 DX(I,J)=0.
      DO 200 I=1,NN
      EX1=EXPF(X(2)*TIM(I))
      TM1=1.0/EX1-1.0
      CT=X(1)*TM1+X(3)
      CDIF=CT-CON(I)
      CTD=CDIF*TIM(I)
      DX(4,1)=DX(4,1)+CDIF*TM1
      DX(4,2)=DX(4,2)-CTD*X(1)/EX1
      DX(4,3)=DX(4,3)+CDIF
      DX(1,1)=DX(1,1)+TM1*TM1
      DX(3,1)=DX(3,1)+TM1
      TM1=TM1*TIM(I)
      DX(2,1)=DX(2,1)-CTD/EX1-TM1*X(1)/EX1
      DX(2,2)=DX(2,2)+CTD*X(1)*TIM(I)/EX1+(X(1)*TIM(I)/EX1)**2
      DX(3,2)=DX(3,2)-X(1)*TIM(I)/EX1
      IF(SENSE SWITCH 4) 130,200
  130 CON(I)=CT
  200 FUNC=FUNC+CDIF*CDIF
      DX(3,3)=NN
      DX(1,3)=DX(3,1)
      DX(1,2)=DX(2,1)
      DX(2,3)=DX(3,2)
      PRINT 250,FUNC
  250 FORMAT(6H FUNC=,E15.7)
      PUNCH 260,FUNC,X
  260 FORMAT(/6H FUNC=,E15.7,6H   XI=,3E15.7)
      DEN=DET(1,2,3)
      DELT(1)=DET(4,2,3)
      DELT(2)=DET(1,4,3)
      DELT(3)=DET(1,2,4)
      DO 300 I=1,3
  300 X(I)=X(I)-DELT(I)*RED/DEN
      IF(SENSE SWITCH 4) 307,314
  314 IF(SENSE SWITCH 1) 315,115
  307 PUNCH 308,(TIM(I),CON(I) ,I=1,NN)
  308 FORMAT((F22.2,F8.4))
  315 PUNCH 316
  316 FORMAT(36HI DXI1             DXI2             DXI3)
      K=4
      PUNCH 302,K,(DX(4,J),J=1,3)
```

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```
      DO 301 I=1,3
      IN=4-I
  301 PUNCH 302,IN,(DX(IN,J),J=1,IN)
  302 FORMAT(I1,3E15.7)
   28 PUNCH 30,DEN,DELT
   30 FORMAT(8H  DENOM=,E15.7,7H DELTA=,3E15.7)
      GO TO 115
      END
C
C
C                    FUNCTION SUBPROGRAM
C          TO CALCULATE THE DETERMINANT OF A 3X3 MATRIX
C               CHOSEN FROM A 4X3 MATRIX
C
      FUNCTION DET(K,L,M)
      DIMENSION D(4,3)
      COMMON D
      DET=0.
   99 DO 100 NN=1,3
      IMP=K
      K=L
      L=M
      M=IMP
  100 DET=DET+D(K,1)*(D(L,2)*D(M,3)-D(M,2)*D(L,3))
      RETURN
```

RESULTS

```
 FUNC=  1.5678614E-03   XI= -1.6287287E+00  3.8877700E-03  4.1270957E-02
 FUNC=  1.5678577E-03   XI= -1.6287287E+00  3.8877696E-03  4.1270982E-02
C                  TIME  OD CALC    OBS
                   0.00   .0412    0.022
-                  3.20   .0614    0.053
                  21.75   .1733    0.180
                  51.80   .3383    0.357
                  81.10   .4817    0.498
                 208.40   .9455    0.946
                 310.30  1.1825    1.168
                 474.80  1.4128    1.400
                 671.20  1.5501    1.555
                 978.60  1.6337    1.642
I DXI1           DXI2             DXI3
4  8.1600000E-08  2.1600000E-06 -1.0000000E-09
3 -4.5485112E+00  7.4328460E+02  1.0000000E+01
2 -4.4318717E+02  8.2766024E+04
1  3.4358139E+00
  DENOM=  2.6569280E+05 DELTA=  2.4678545E-02  1.1582770E-04  2.5891994E-03
```

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The computer programs as written did not run spectacularly well, although they eventually avoided overflows, underflows, and non-convergence of the iteration long enough to give reasonable results. The chief problem is undoubtedly computational error, especially from the brute-force method of calculating determinants. Use of double-precision arithmatic and a reordering of some of the computations in line with standard numerical techniques [1] should help a great deal.

A contributing factor to the frequent divergence in fitting the 0.2 N data is that the conditions were close to such that the equation being fit no longer applied. Since $k_1+k_2 = 3.94\times10^{-3}hr^{-1} \simeq 3.73\times10^{-3}hr^{-1} = k_3$, and since X_1 and X_3 both contain factors of $1/(k_1+k_2-k_3)$, the iteration could easily blow up if started very far from the solution.

---

1 Peter A. Stark, "Introduction to Numerical Analysis", Macmillan, New York, 1970

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Appendix II

Elemental Analyses and Spectra

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Elemental Analyses

		%C	%H	%N	%P
Ph(H_2enePDA)	Calc.	48.48	5.60	14.13	15.63
	Found	48.51	5.54	13.92	15.52
Ph(MeHenePDA)	Calc.	50.94	6.18	13.20	14.60
	Found	50.83	6.23	13.01	14.91
Ph(Me_2enePDA)	Calc.	53.10	6.68	12.38	13.69
	Found	53.20	6.64	12.41	13.51
Ph(Et_2enePDA)	Calc.	56.68	7.53		12.18
	Found	56.92	7.51		12.32
Ph(i-Pr_2enePDA)	Calc.	59.56	8.21		10.97
	Found	59.24	8.41		11.54
Ph(t-Bu_2enePDA)	Calc.	61.92	8.77		9.98
	Found	61.82	8.74		10.13
Ph(Ph_2enePDA)	Calc.	68.56	5.47	7.99	8.84
	Found	68.55	5.47	8.09	9.04
Cl(Me_2enePDA)	Calc.	28.50	5.98		18.38
	Found	28.29	6.15		18.29
$H_3^+NCH_2CH_2NHPO_3^-Ph$	Calc.	44.45	6.06		
	Found	43.38	5.95		

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Ultraviolet Spectra

		shldr	max	min	max	
Ph(H_2enePDA)	λ	256	260	264	266	nm
in H_2O	ε	270	325	240	260	

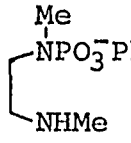
		max	min	max	min	max	
Ph(Me_2enePDA)	λ	255	257	260	264	266	nm
in H_2O	ε	268	264	328	216	254	

		max	min	max	min	max	
Ph(i-Pr_2enePDA)	λ	256	258	261	265	267	nm
in H_2O	ε	316	312	400	270	320	
	λ	257	259	262	266	268	nm
in MeOH	ε	336	334	450	310	370	

		max	min	max	min	max	
Ph(t-Bu_2enePDA)	λ	256	258	262	266	267	nm
in H_2O	ε	400	380	525	320	425	

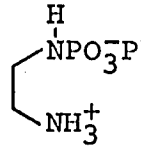
		max	maxima	
Ph(Ph_2enePDA)	λ	241	265-275	nm
in MeOH	ε	3.1×10^4	$2.2\text{-}2.5\times10^3$	

		shldr	max	min	max	min	shldr	max
in 20% MeOH/H_2O	λ	282	274	270	267	263	260	242
	$10^{-3}\epsilon$	1.59	2.15	2.11	2.14	1.97	2.08	29



		shldr	max	shldr	
in 5N KOH	λ	257	262	267	nm
	ε	430	525	460	

		max	min	max	
PhO^- in 1N NaOH	λ	234	260	287	nm
	ε	10^4	660	2.58×10^3	



		min	shldr	max	shldr
in H_2O	λ	232	257	261	266
	ε	47	350	427	380

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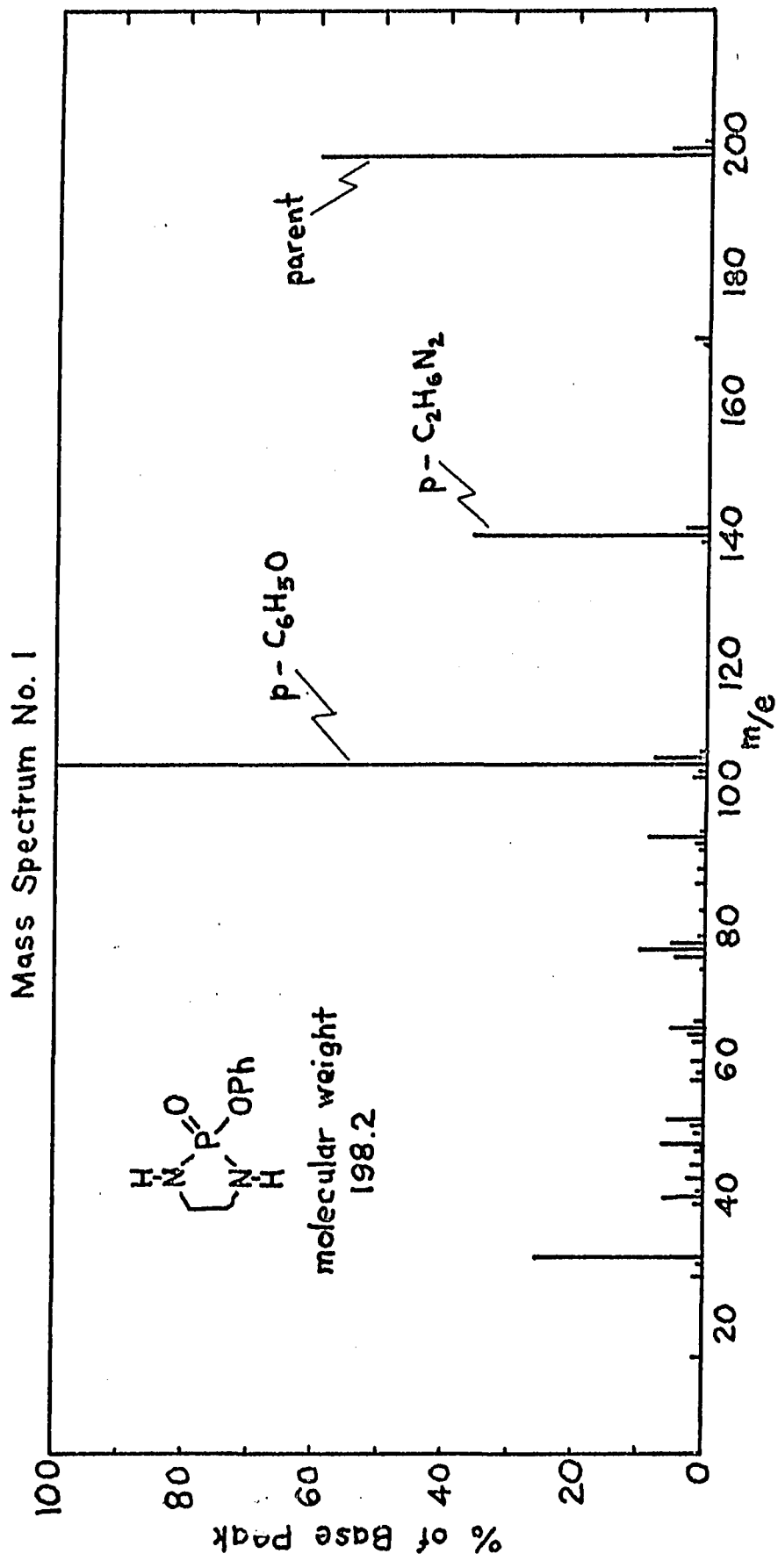

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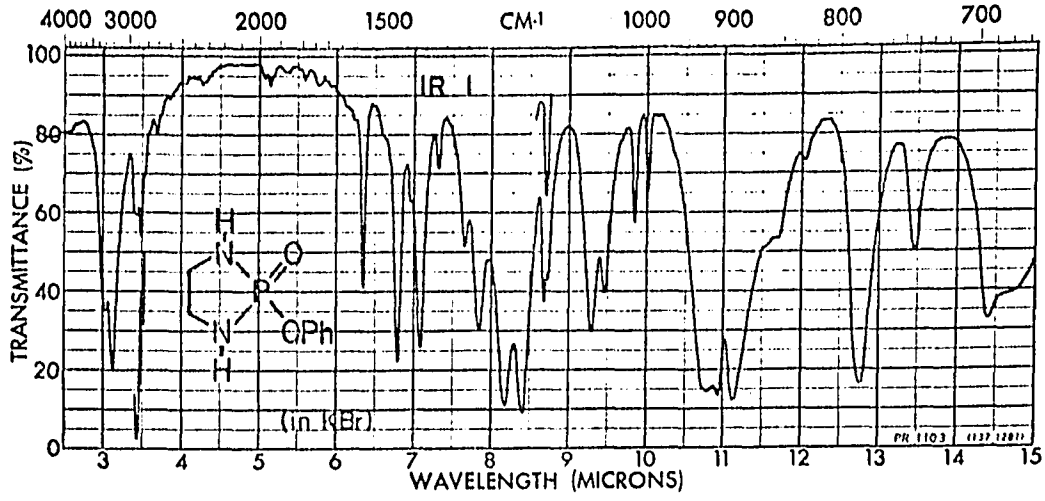

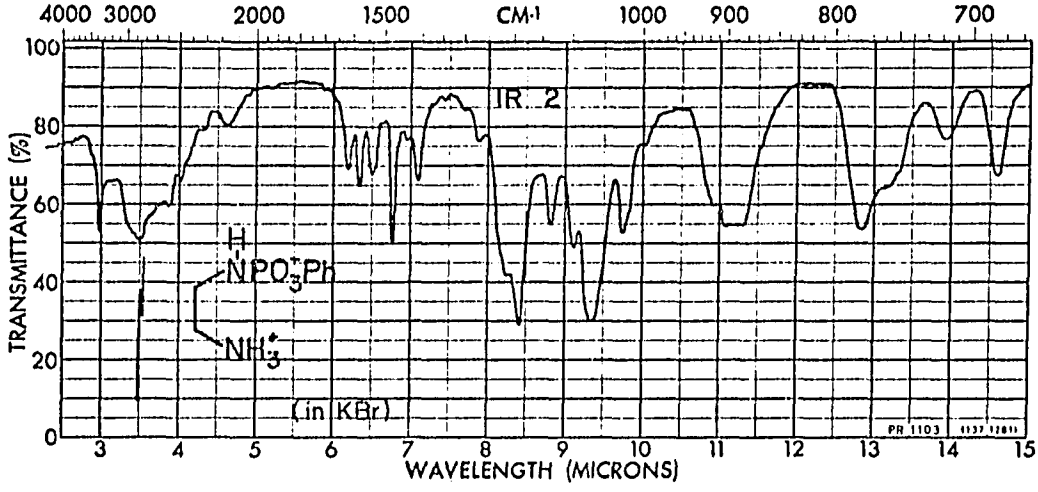

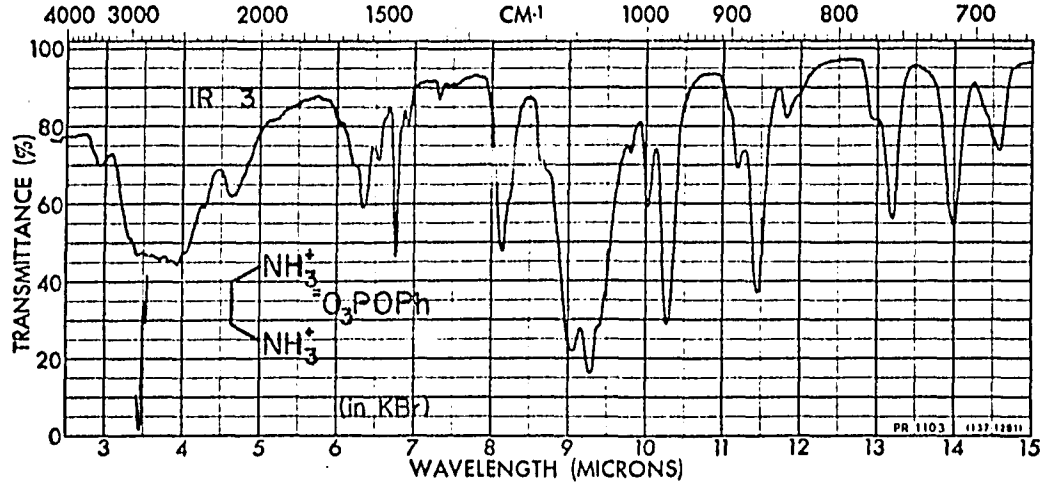

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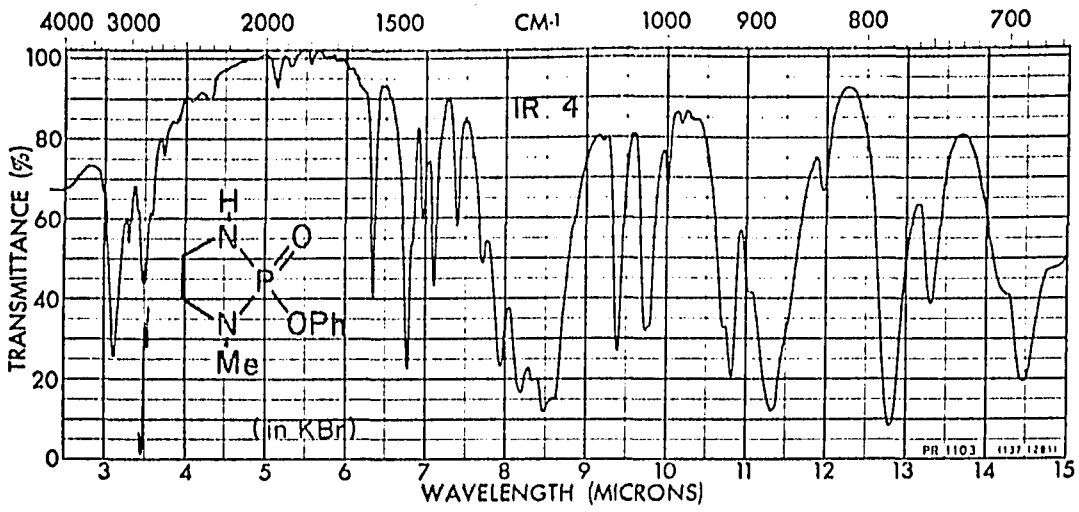

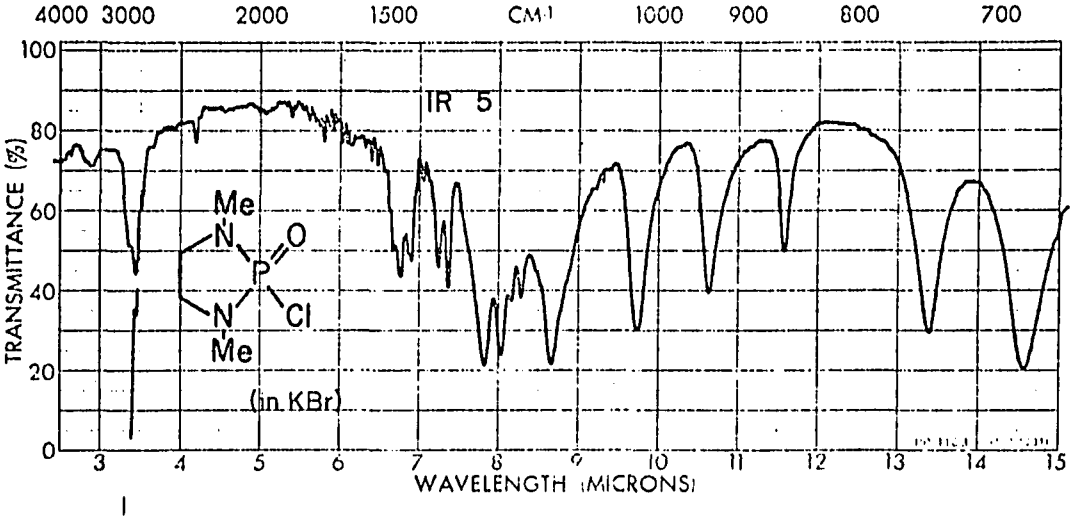

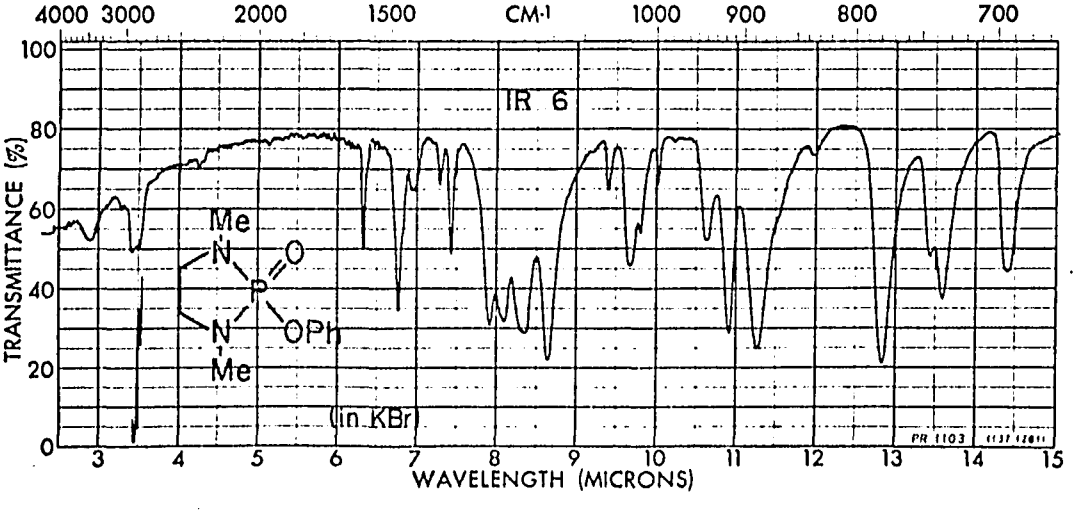

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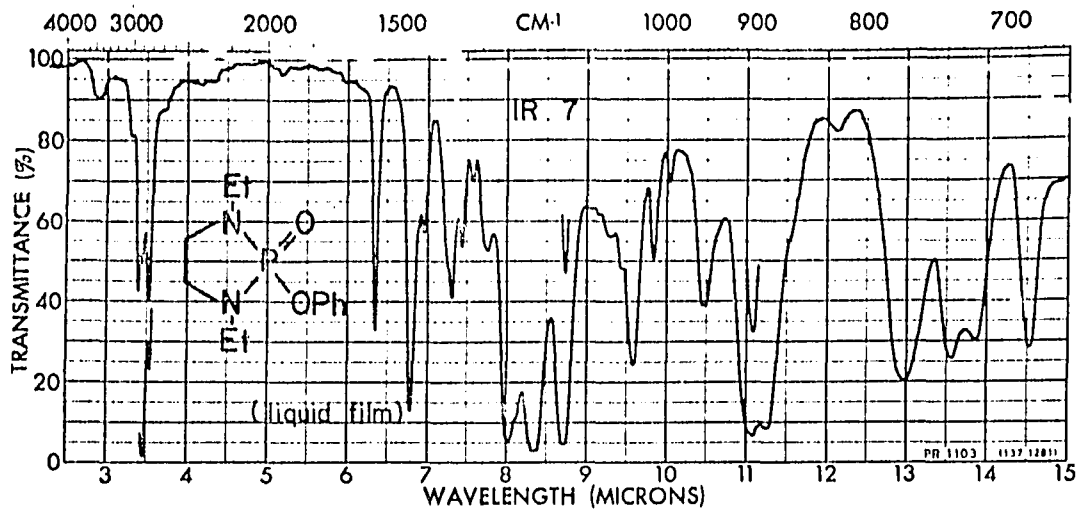

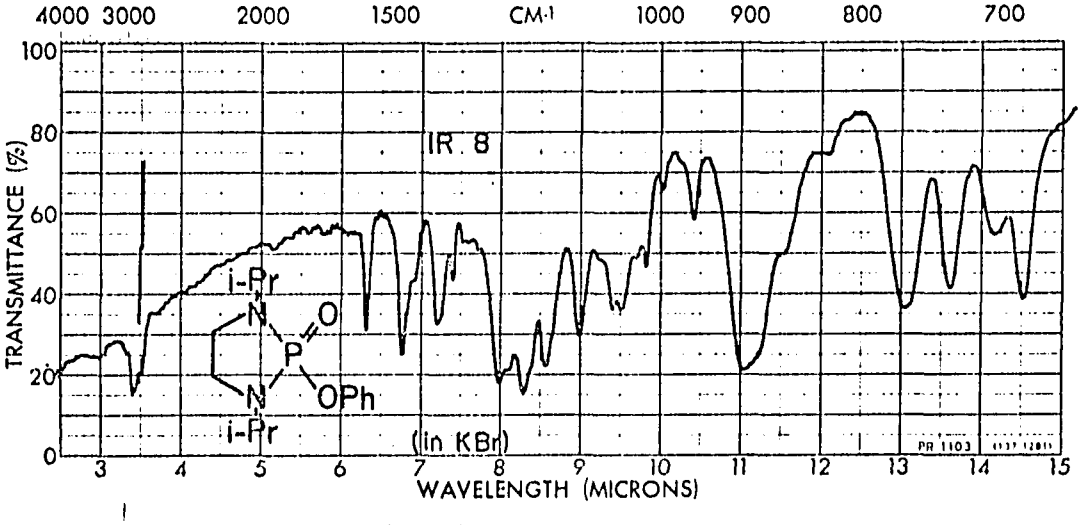

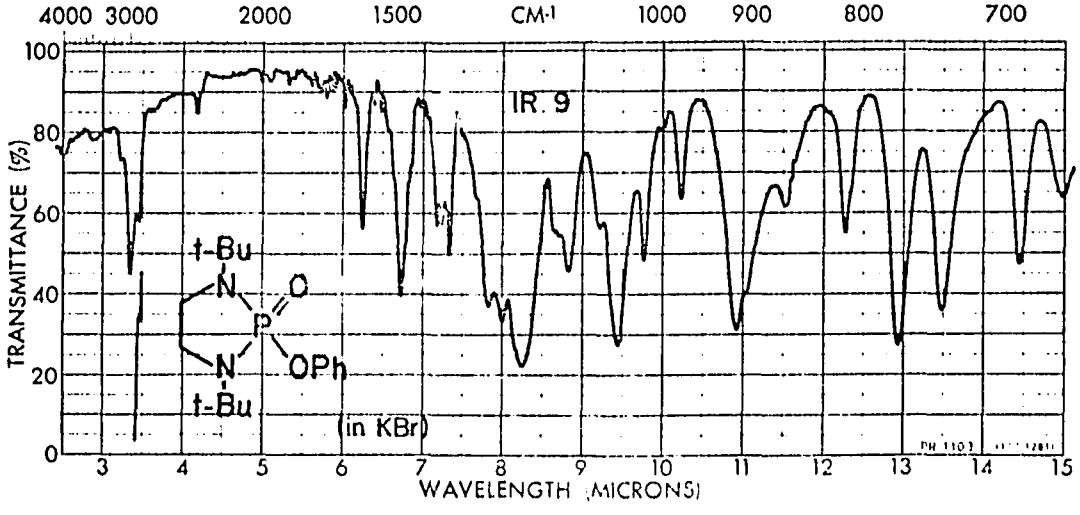

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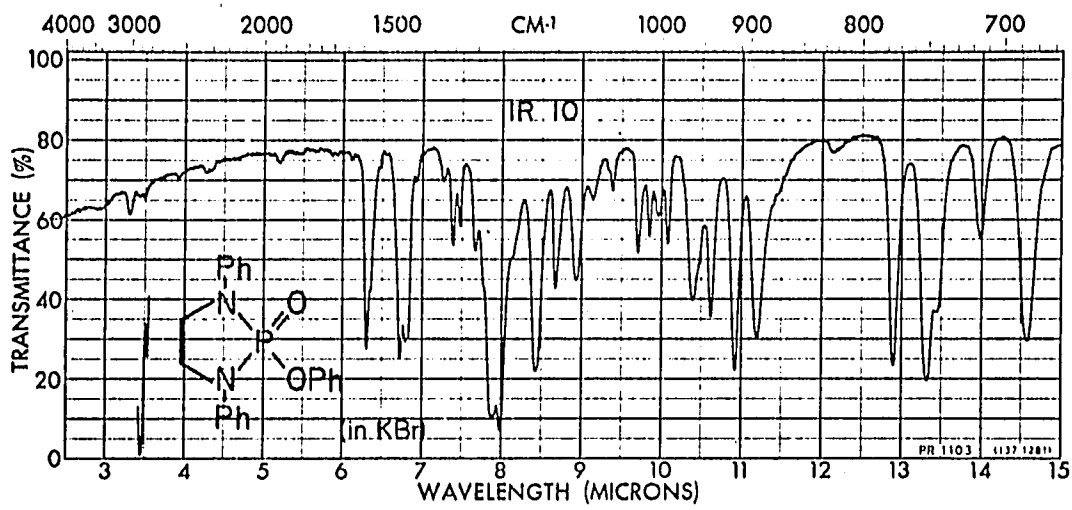

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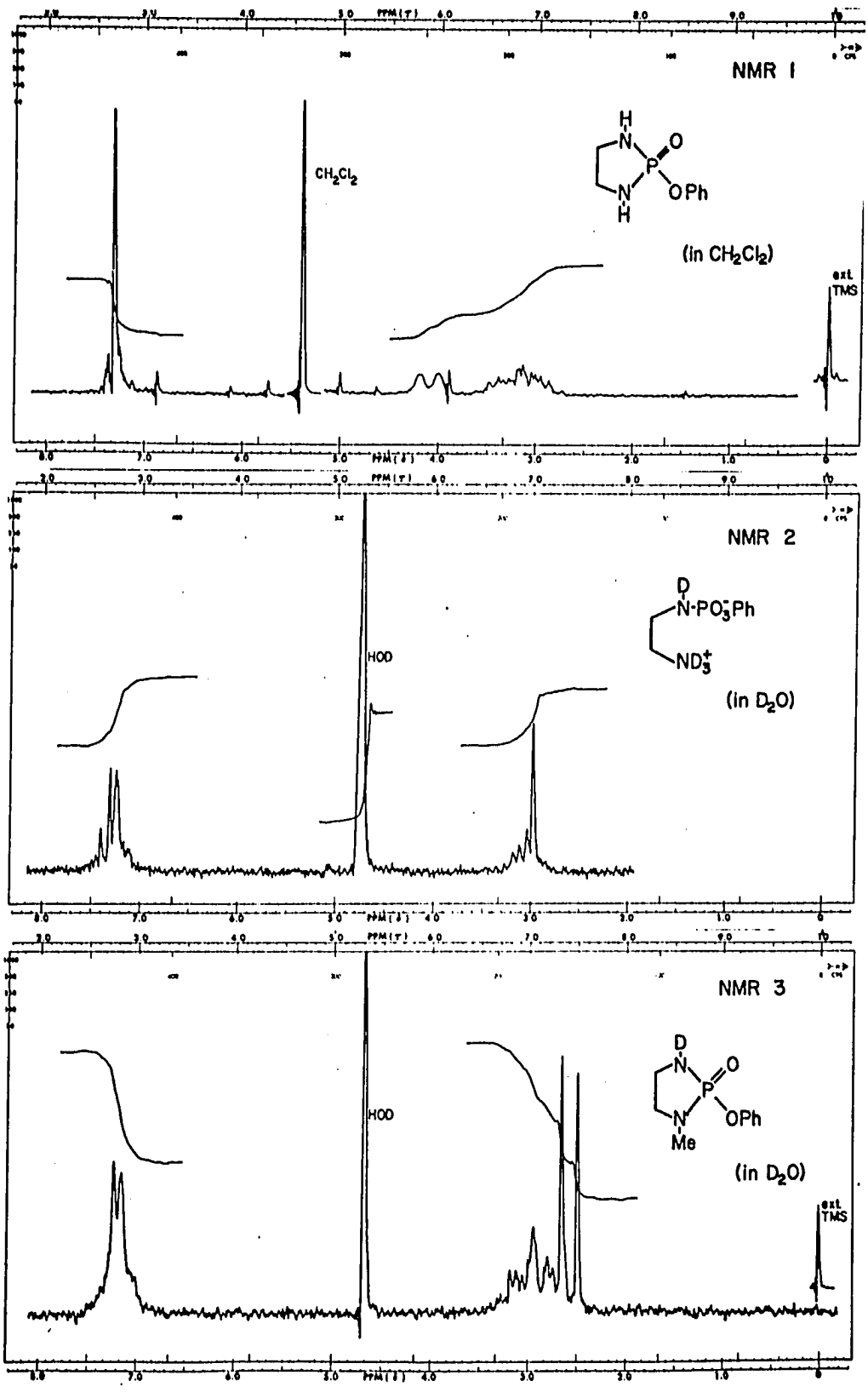

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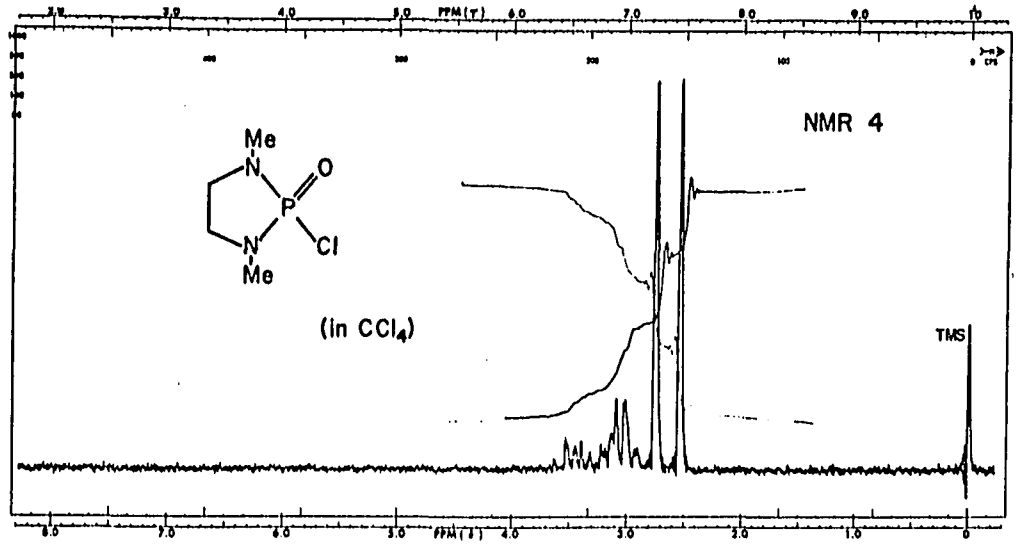

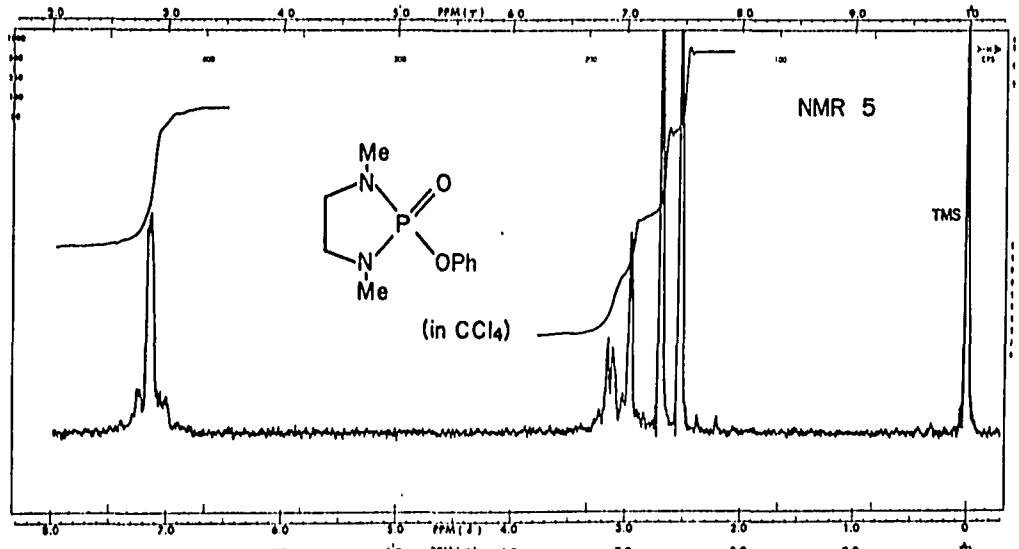

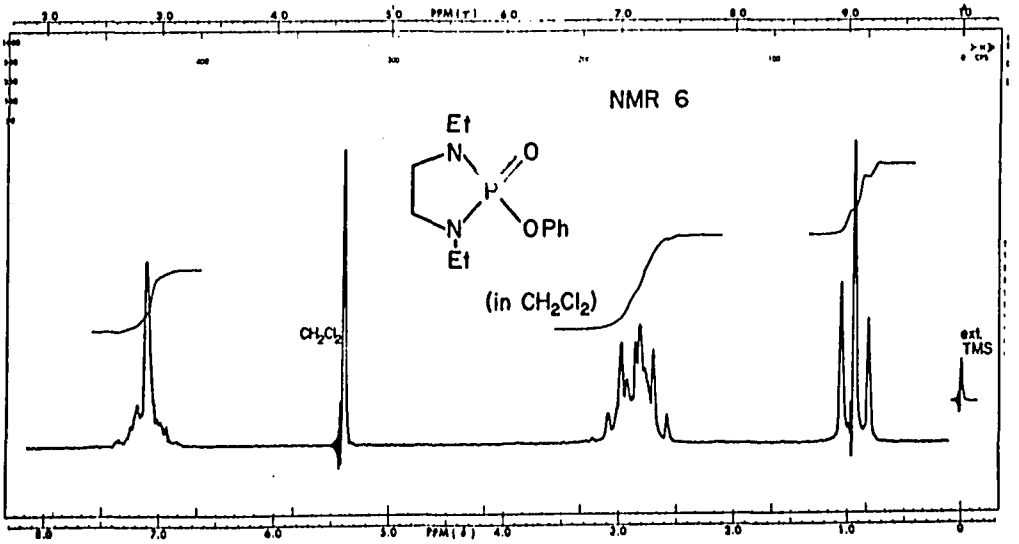

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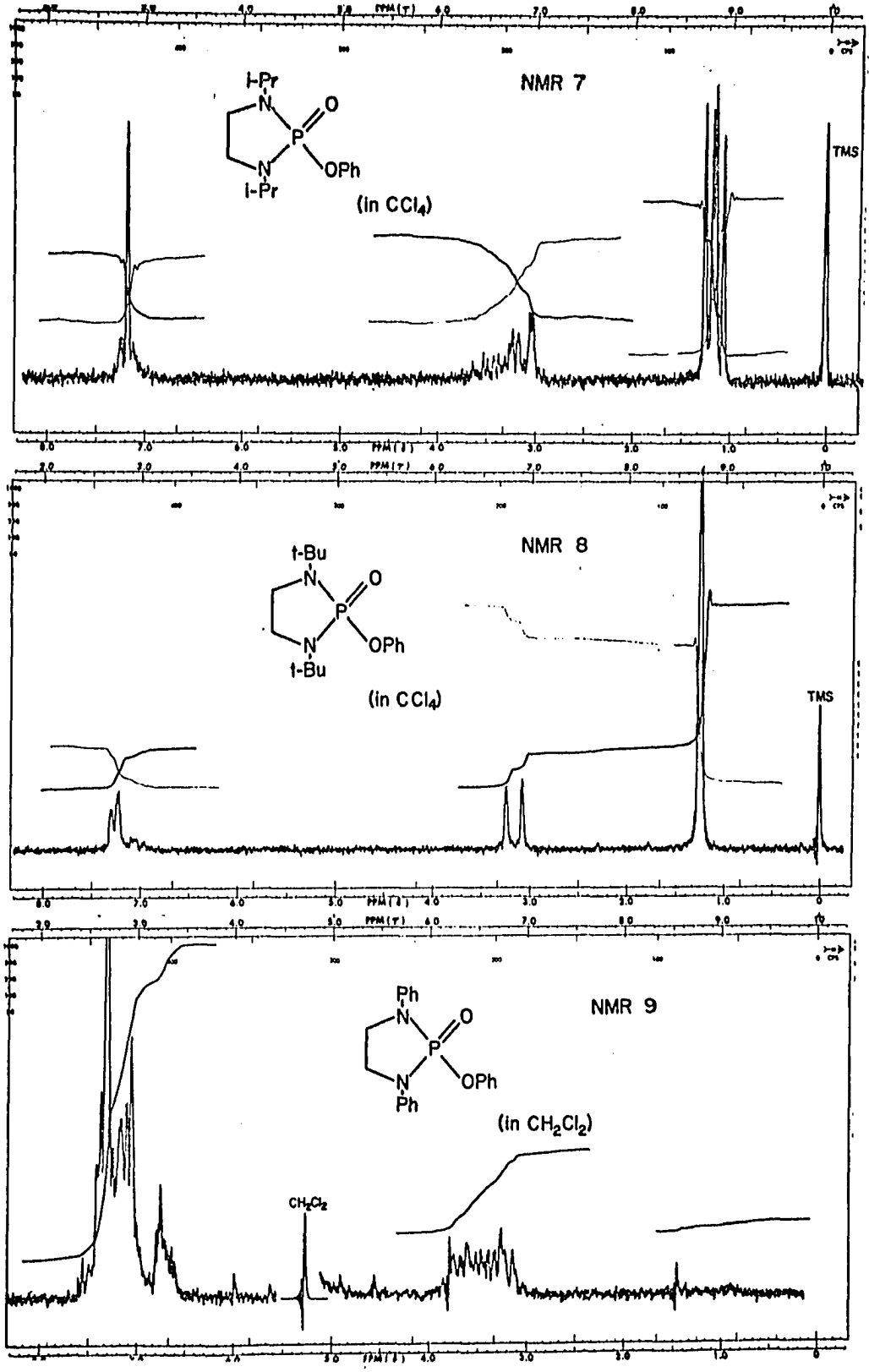

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