REACTIVITY STUDIES OF

PHOSPHORIC AMIDES AND ESTERS

a thesis submitted to the

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DOCTOR OF PHILOSOPHY

by

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ABSTRACT

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The effect of protonation and Lewis acid-base interaction on the ^1H n.m.r. chemical shifts of the ester and amide bonds in selected phosphoramidates $(RO)_2P(O)NR'_2$ was investigated. The results are interpreted in terms of the interaction of the phosphoryl oxygen atom with Lewis acids and oxygen/nitrogen diprotonation in trifluoromethanesulphonic acid.

Intramolecular nucleophilic displacement of the halide ion from secondary β-chloroethyl-substituted phosphoramidates $X_2P(O)NHCH_2CH_2Cl$, diamidates $(RO)(MeNH)P(O)NHCH_2CH_2Cl$, and β-chloroethyl phosphates $Y(MeO)P(O)OCH_2CH_2Cl$, was studied under conditions of electrophilic (Ag^+) and basic (NaH) catalysis. 1,3-Substitution by the nitrogen atom of the phosphoramidates, yielding ethylenimine derivatives, was found to be the preferred reaction pathway; the alternative 1,5-reaction involving the amide nitrogen or phosphoryl oxygen atoms was not observed. No intramolecular nucleophilic displacement occurred in the β-chloroethyl phosphate esters. The reaction of the N-(β-chloroethyl)-substituted phosphoramidates with alkyl halides and sodium hydride, yielding N-phosphorylated ethylenimines $X_2P(O)\overline{NCH_2CH_2}$ together with the N-alkylated product, demonstrated the comparable reactivity of the conjugate base of these substrates towards intra- and intermolecular alkylation.

The mass spectra of forty-four organophosphorus compounds containing both the phosphate ester $\rangle P(O)OR$ and phosphoramidate $\rangle P(O)NR'R''$ functional groups were recorded and interpreted. Attention was focussed on P-N bond cleavage. This was shown to occur *via* three different pathways: (i) simple homolytic fission yielding a phosphorylium ion and an amino radical (or a phosphorylium radical and an amino cation), (ii) fission accompanied by hydrogen migration from the ester group yielding an amine radical ion and a neutral phosphite species, and (iii) P-N bond fission accompanied by migration of the ester R

group from oxygen to the departing nitrogen yielding a substituted amine radical ion and a metaphosphate species. Fragmentation pathways characteristic of the N-(β-chloroethyl) derivatives (phosphorylated nitrogen mustards), O-(β-chloroethyl) derivatives, as well as the N-phosphorylated ethylenimines, are also presented.

Rates and products of the base-catalysed hydrolysis of some amidoesters of phosphoric acid were determined. In the N,N-dimethyl derivative the P-O bond was deactivated towards hydrolysis relative to the reference substrate, trimethyl phosphate, while the P-N bond was resistant to attack by nucleophiles. The reactivity of the ester linkage of the N-methyl derivative was similar to that in trimethyl phosphate and it is proposed that hydrolysis occurred in this case *via* an E1cb pathway. In the N-ethylene derivative both the P-O and P-N bonds were strongly activated towards nucleophilic substitution, the P-N bond being hydrolysed at a rate somewhat faster than the P-O bond. The much greater reactivity of the N-phosphorylated ethylenimine relative to the N,N-dimethylamino derivative is interpreted in terms of the absence of any significant $d_{\pi} - p_{\pi}$ overlap between the phosphoryl group and the nitrogen atom of the ethylenimine ring. The N-(β-chloroethyl) phosphoramidate reacted *via* fast base-catalysed cyclisation to the N-ethylene phosphoramidate. The reactivity of these substrates towards other nucleophiles such as water, methoxide ion and fluoride ion was also investigated.

The crystal and molecular structure of N-(β-chloroethyl)diphenylphosphinamidate $Ph_2P(O)NHCH_2CH_2Cl$ showed that the nitrogen and chlorine atoms were gauche. This is not a favourable conformation for the observed 1,3-attack at the β-carbon by the nitrogen atom which was found to occur in solution. The gauche conformation results from the *trans*-polymeric hydrogen bonding which occurs in the crystal lattice. The crystal structure of N-ethylene diphenyl-phosphinamidate $Ph_2P(O)\overline{NCH_2CH_2}$ revealed that the nitrogen atom was significantly

pyramidal. This is in contrast with the nearly planar nitrogen atom reported for the N,N-dimethyl analogue and could be taken as evidence for the absence of $d_{\pi} - p_{\pi}$ overlap between the phosphoryl group and the nitrogen atom in the N-phosphorylated ethylenimines. The P-N bond distances in both the N-ethylene and N,N-dimethyl diphenylphosphinamidates are practically identical, indicating similar P-N bond orders in both substrates. The comparison of molecular parameters with reactivities of base-catalysed hydrolysis leads to the conclusion that the net bonding requirements of the ethylenimine substituent not only increase the pyramidality of the nitrogen atom but also result in the weaker electron-donating ability of the $\overline{\text{NCH}_2\text{CH}_2}$ group (relative to that of the NMe_2 group), thus giving rise to the greater reactivity of the phosphoryl centre in N-phosphorylated ethylenimines.

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This work is dedicated to my husband, Selwyn.

PUBLICATIONS

1. B. Davidowitz and T.A. Modro, Phosphoric Amides. Part 2. ^{1}H N.M.R. Investigation of the Acid-Base Behaviour of Phosphoramidates, *S. Afr. J. Chem.*, 33, 74 (1980).

2. B. Davidowitz and T.A. Modro, Phosphoric Amides. Part 6. Intramolecular Nucleophilic Displacement in β-Haloethylsubstituted-Phosphoramidates, *S. Afr. J. Chem.*, 35, 63 (1982).

3. B. Davidowitz and T.A. Modro, Phosphoric Amides. 7. Mass Spectrometry of Phosphoric Amidoesters: Fragmentation Patterns and Migratory Aptitudes, *Org. Mass Spectrom.*, 19, 128 (1984).

4. B. Davidowitz and T.A. Modro, Phosphoric Amides. 8. The Effect of the Ethylenimine Substituent on the Solvolytic Reactivity of Phosphate and Phosphoramidate Bonds, *J. Chem. Soc., Perkin Trans. 2*, in press.

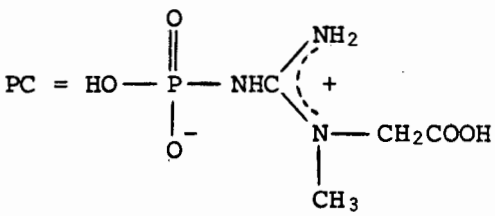
5. B. Davidowitz, T.A. Modro and M.L. Niven, Phosphoric Amides. 9. Crystal and Molecular Structure of N-Diphenylphosphinylethylenimine and its Precursor, N-(β-chloroethyl)diphenylphosphinamidate, in preparation.

CHAPTER ONE

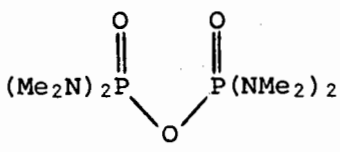
INTRODUCTION

Phosphoramidates are an important class of phosphorus compounds and there is considerable interest in their chemistry. The lability of the P-N bond plays an important role in biological phosphorylations of various substrates. One of the most notable examples is N-phosphorocreatine, PC, which is found in varying quantities in most vertebrate tissue. This naturally-occurring phosphoroguanidate functions as a phosphagen and plays a vital role during muscle contraction.[1] It maintains a constant concentration of ATP by phosphorylation of ADP in a rapid, creatine kinase-catalysed reaction (Eq. 1).

$$H^+ + ADP + PC \xrightleftharpoons{Mg^{2+}} ATP + creatine \qquad (1)$$



The insecticide Schradan (1, octamethyl pyrophosphoramidate) was described by Schrader in 1941 and was the first systemic phosphate insecticide to be recognised.[2a] Ruelene[2b] (2) [O-methyl O-(4-tert.-butyl-2-chlorophenyl) N-methyl phosphoramidate] and Nellite[2c] (3, O-phenyl N,N'-dimethyl phosphoramidate) are other commercially available pesticides which contribute to this class of compounds.



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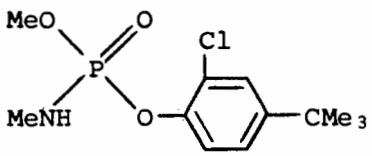

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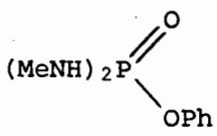
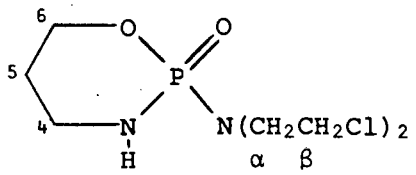


(3)

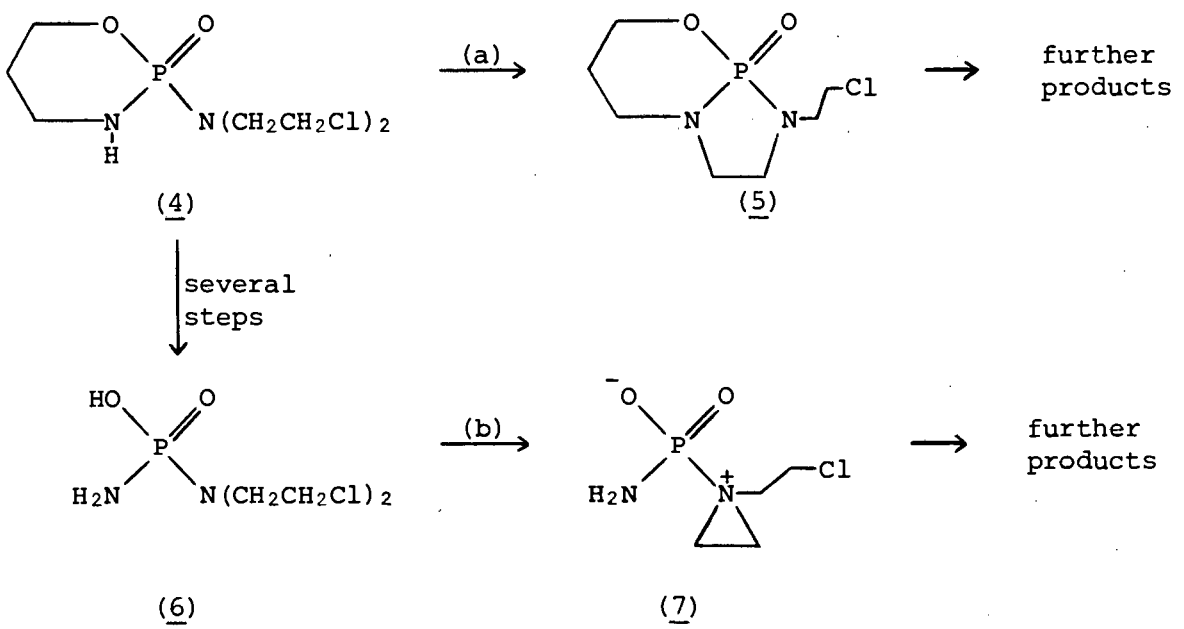
Cyclophosphamide, 2-[bis(2-chloroethyl)amino]-2*H*-1,3,2-oxazaphosphorinane-2-oxide (4), exhibits clinical effectiveness against a wide spectrum of human cancers.[3]



(4)

Cyclophosphamide itself exhibits little cytotoxic behaviour; the anticancer activity of (4) is based on the release of nornitrogen mustard, $HN(CH_2CH_2Cl)_2$, after *in vivo* activation of the substrate molecule.[4] Intensive research on the *in vivo* and *in vitro* transformations of (4) has been carried out and two intramolecular nucleophilic displacements of the β-chlorine atom [Scheme 1, pathways (a) and (b)] have been described.

The first of these, pathway (a), involves the endocyclic nitrogen of (4) and results in a bicyclic product (5) which then undergoes further degradation;[5] pathway (b) involves the 1,3-cyclisation of the phosphoramide mustard (6) to give the ethyleniminium derivative (7) (Scheme 1).[6] The phosphoramide mustard (6) is a potent alkylating agent at physiological pH.[7]



Scheme 1

The relative rate at which pathways (a) and/or (b) occur depends on the nucleophilicity of the two phosphoramidate nitrogens with respect to the β-carbon atom.

The acid-catalysed phosphorylating reactivity of phosphoramidates (8) is related closely to their protonation equilibria in which they may behave as either oxygen- or nitrogen-bases (Eq. 2).

$$\underset{(8)}{X(Y)P(O)NR_2} \overset{H^+}{\rightleftharpoons} \underset{(9)}{X(Y)\overset{+}{P}(OH)NR_2} \quad \text{or} \quad \underset{(10)}{X(Y)P(O)\overset{+}{N}HR_2} \qquad (2)$$

The structure of the protonated form has not yet been determined owing to the low stability of compounds (8) in acidic solutions. Reactivity studies[8] indicate that (10) is a reactive intermediate in hydrolytic reactions. On the other hand MO calculations[9] and molecular structure determinations[10] demonstrate that O-protonation of the amide function (9) is preferred. It has been shown that the P-N bond in (8) is stable in trifluoromethanesulphonic acid and the behaviour of these compounds could be interpreted in terms of an oxygen/nitrogen diprotonated form, $X(Y)\overset{+}{P}(OH)\overset{+}{N}HR_2$, derived from compounds (8) as a kinetically important species.[11]

In the present study on the basicity of (8) an approach was used in which the difference between the ^1H n.m.r. chemical shifts of the α- and β-hydrogen atoms of selected compounds was utilised as a probe of their protonation behaviour.[12] It was assumed that in phosphoramidates of type (11) the chemical shifts of the β-methyl hydrogens of the ethoxy-groups would be affected much less by protonation than the α-hydrogens of the ethoxy- and N-methyl groups (see Eq. 3).

$$(CH_3CH_2O)_2P(O)NRCH_3 \xrightleftharpoons{H^+} (CH_3CH_2O)_2\overset{+}{P}(OH)NRCH_3$$

(11) (12)

or (3)

$$(CH_3CH_2O)_2P(O)\overset{+}{N}HRCH_3$$

(13)

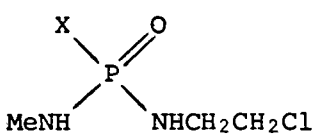
Phosphoryl compounds behave as strong oxygen bases towards Lewis acids with the phosphoryl oxygen acting as a donor centre.[13] Shielding effects[14] parallel to those operating in structure (12) were investigated using the titanium(IV) chloride complexes (14) (see Eq. 4).

$$(11) \xrightleftharpoons{TiCl_4} (CH_3CH_2O)_2\overset{+}{P}(OTiCl_4)^-NRCH_3 \quad (4)$$

(14)

The results of these basicity studies are presented in Chapter 2.

As well as being a base the $\rangle P(:O)N\langle$ system in phosphoramidates has to be considered as an ambident nucleophile in which nucleophilic reactivity is possible *via* the amidate nitrogen atom as well as the phosphoryl oxygen atom. In the N-(β-chloroethyl) N-methylphosphorodiamidate (15) intramolecular



(15)

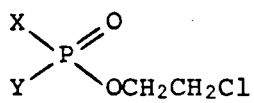
displacement of a chloride ion can in principle involve one or other of the nitrogen atoms leading to formation of a 3- or 5-membered cyclic derivative, or the phosphoryl oxygen atom; each reaction giving rise to different products. Although nucleophilic reactivity of both the nitrogen atom and phosphoryl oxygen atom with respect to alkylating agents has been observed for various phosphoric amides,[15] all reactions studied concerned bimolecular

(intermolecular) alkylations of the organophosphorus substrates. As far as intramolecular substitution reactions are concerned, however, both the intrinsic nucleophilicity of individual atoms and conformational and entropy factors are expected to determine the course of the reaction.

Thus the preferred pathways of nucleophilic displacement of the halide ion in the β-chloroethyl derivatives of phosphorodiamidates (15), phosphoramidates (16) and phosphoric acid esters (17) were investigated under various conditions.

$X_2P(O)NHCH_2CH_2Cl$

(16)

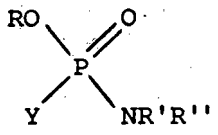


(17)

The N-(β-chloroethyl) group is an integral part of compounds (15) and (16) as well as of cyclophosphamide (4). The results of these studies on intramolecular alkylation reactions were related to the reactions of (4) as outlined in Scheme 1 and are discussed in Chapter 3.

The behaviour of phosphoramidates under conditions of electron impact has received limited attention.[16] In systems containing heteroatoms ionisation of the electrons of the heteroatom is preferred.[17] The charge on the molecular ion is thus located in the $\rangle P(O)N\langle$ moiety conferring an element of uniformity on the fragmentation pathways of these compounds. This localised charge concept is important in the rationalisation of mass spectral fragmentations. The ability to predict which bonds are likely to break in a given class of compounds is of great value in the interpretation of the fragmentation pathways of new compounds.

The mass spectra of a series of phosphoramidates of the type (18) were examined.



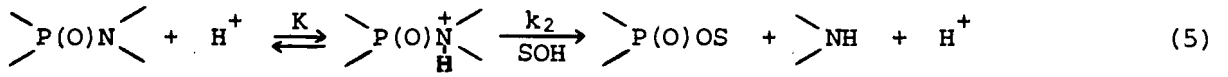
(18)

As an electron is removed from the >P(O)N< function these spectra provide an indication of the distribution of electrons as well as the behaviour of electron deficient phosphoramidates in the gaseous phase where no solvent interactions are possible.

Simple cleavage of the P-N bond has been observed[16,18] and in this respect substrates (18) parallel the behaviour of carboxylic amides.[19] Hydrogen migration to give an amine radical ion accompanied by release of a neutral phosphite molecule has also been observed.[20] P-N bond cleavage accompanied by O→N migration, can be related to the well known electron impact-induced fragmentation of carbonates[21] and carbamates.[22]

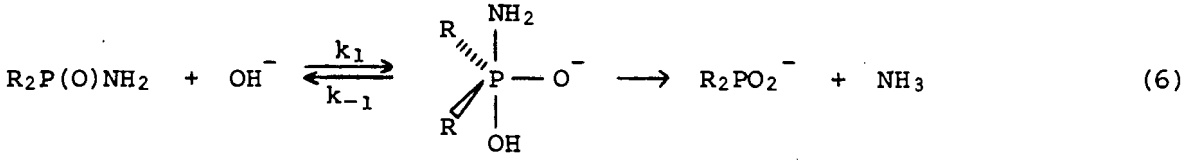
The investigation of the mass spectra of compounds (18) was carried out to provide more general information on the mass spectrometry of phosphoramidates. Attention was focussed on P-N bond cleavage and possible migrations, as well as on the effects of structure on these fragmentations. The electron impact-induced fragmentations of phosphoramidates containing an N-(β-chloroethyl) group were also determined and compared with those reported for cyclophosphamide (4).[23] These results are presented in Chapter 4.

The acid-catalysed hydrolysis of phosphoramidates[24,25] and phosphinamidates[26] has received much attention and the mechanisms of these reactions are well understood. Detailed investigations carried out by several groups of workers[8,24,27] have demonstrated that the P-N bond is labile under mildly acidic conditions. These compounds hydrolyse *via* N-protonated reactive intermediates which then undergo bimolecular nucleophilic displacement by a solvent molecule (see Eq. 5).



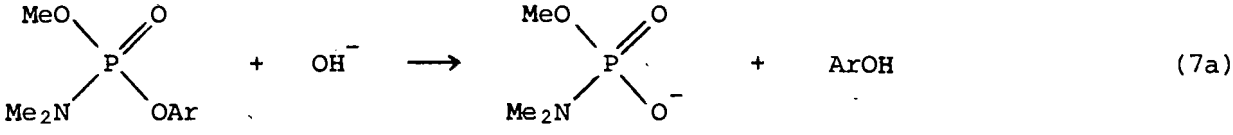
(5)

The lability of the P-N bond under alkaline conditions varies according to the nature of the reacting species. In basic solution phosphinamidates undergo slow P-N bond cleavage by a mechanism involving the formation of a trigonal bipyramid as an intermediate (Eq. 6).[8]



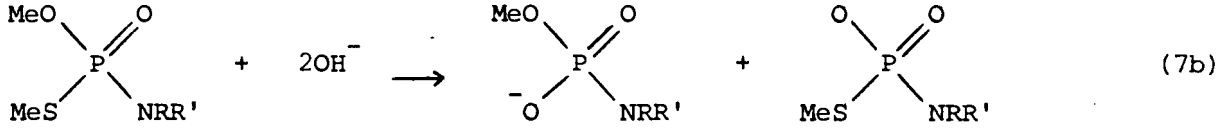
(6)

The acyclic phosphoramidates[28] (19) and phosphoramidothioate esters[29] (20) exhibited no P-N bond cleavage under alkaline conditions (Eq. 7a and 7b).



(7a)

(19) 100% P-O bond fission

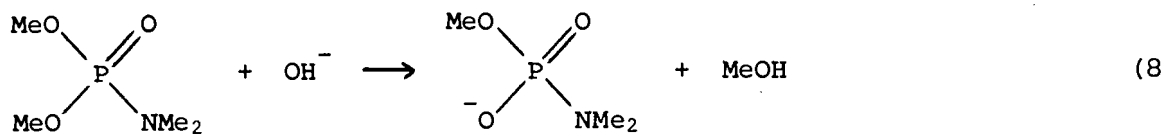


(7b)

(20) (20a) (20b)

The relative amounts of (20a) and (20b) formed during hydrolysis depended on the solvent used in the reaction. P-O bond cleavage occurred since no significant ^{18}O incorporation was found when the reaction was carried out in water enriched with $H_2{}^{18}O$.[29]

The phosphoramidate (21) undergoes both P-O and C-O bond cleavage under alkaline conditions with exclusive release of methanol (Eq. 8).[30]

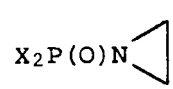


(8)

(21)

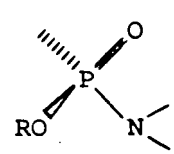
Hamer and Tack[31] investigated the alkaline hydrolysis of a series of aryl methyl phosphoramidates and phosphoramidothioates and found that their results were in accord with an $S_N2(P)$ rather than an Elcb mechanism as the major pathway of the reaction. They also found that increasing the number of methyl groups at nitrogen led to a decrease in the hydrolysis rates for the aryl methyl esters.

The unusual bonding in three-membered rings and the associated angle strain is well-known.[32] The presence of an ethylenimine substituent in the phosphoramidates (22) would be expected to have an effect on the behaviour of these compounds under conditions of alkaline hydrolysis. This aspect of the hydrolysis of phosphoramidates was also investigated and these results are presented in Chapter 5.



(22)

The objectives of this project, then, were to study the properties of the phosphoramidate system (23) using the following approaches:



(23)

i The behaviour of (23) as a base, *i.e.* its reaction with protons particularly in terms of the position of protonation (nitrogen *vs.* oxygen).

ii (23) is an ambident nucleophile (nitrogen and oxygen atoms are potential nucleophiles). Thus intramolecular alkylation reactions with respect to the electrophilic β-carbon atom of an N-(β-chloroethyl) substituent were investigated. Since the N-(β-chloroethyl) group is an important function in the phosphoramidate, cyclophosphamide (4) it was hoped that some insight into the intramolecular reactivity of this compound might be gained.

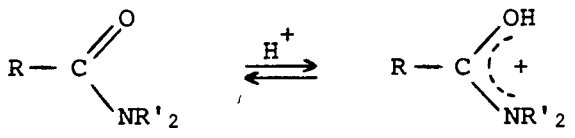
iii Unimolecular collapse of (23) after activation by removal of an electron in the gas phase was studied by mass spectrometry. The detailed mechanisms of fragmentation would be expected to be a function of the structure of the molecular ion resulting from ionisation of the phosphoramidate function.

iv The susceptibility of (23) to attack by a strong nucleophile, OH^-, as a function of substitution at nitrogen was investigated. The relative reactivities of the ester (P-O) and amide (P-N) bonds and structural effects on these reactivities were of particular interest.

v Molecular parameters of (23) have been determined by X-ray crystal structure analysis for selected substrates in collaboration with Dr. M. Niven of the Department of Physical Chemistry, U.C.T. and the results are discussed in Chapter 6.

2.1 INTRODUCTION

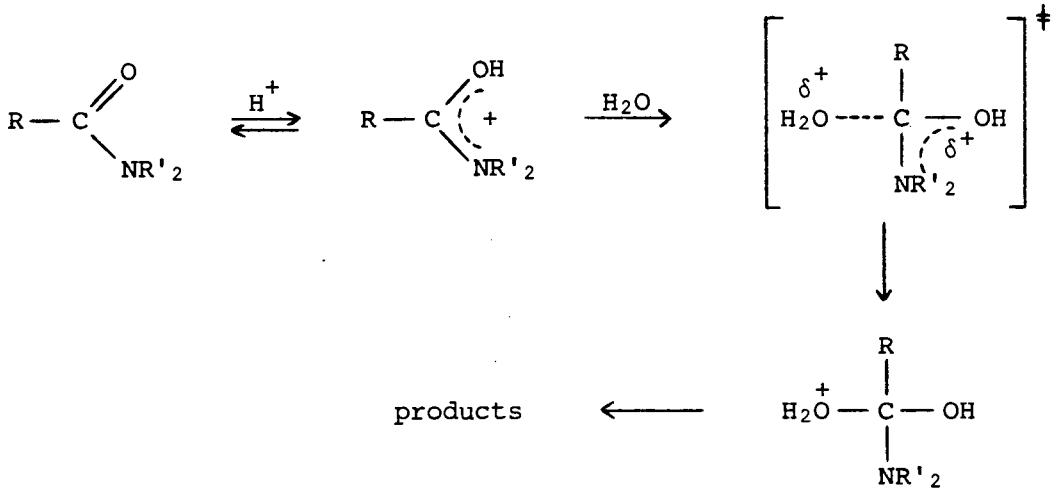
The site of protonation (oxygen *vs.* nitrogen) in carboxylic amides has been investigated for many years. It is now known that the predominant form at all acidities is the O-protonated amide (24) (Eq. 9).[33]



(9)

(24)

The hydrolysis of amides under acidic conditions is interpreted in terms of an A_o^T2 mechanism in which the rate-determining step is formation of an oxonium-type tetrahedral intermediate (25) from the O-protonated form of the conjugate acid of the substrate (Eq. 10).[34]

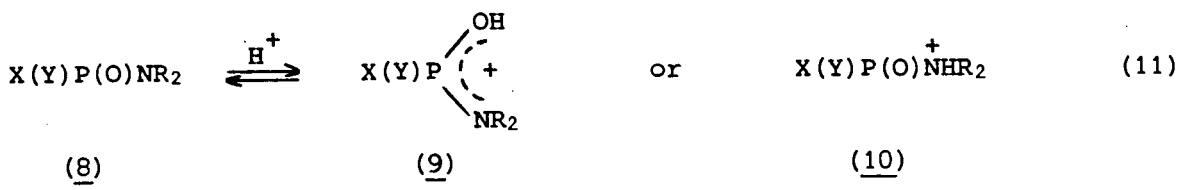


(10)

(25)

Carboxylic amides undergo hydrolysis much more slowly than esters as NR'_2 is a poor leaving group, therefore more vigorous conditions are normally required.[35]

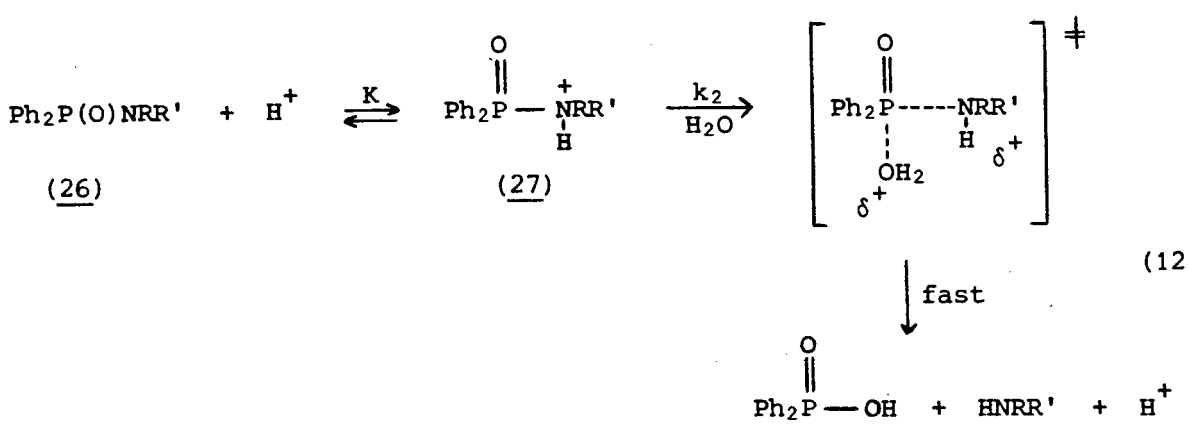
Phosphoramidates (8) also have two potential protonation sites namely the phosphoryl oxygen giving rise to structure (9) and the amidate nitrogen atom structure (10) (Eq. 11).



(8) (9) (10) (11)

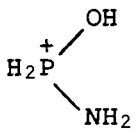
Under conditions of acid hydrolysis (10) would be expected to be much more reactive than (9) as (9) is resonance stabilised and must undergo proton transfer in order to have a good leaving group. Phosphoramidates are not stable in aqueous acid. Thus it is not possible to study their acid-base behaviour by conventional measurements of ionisation ratios of the substrates in aqueous acids of varying strength and indirect methods must be used.

Koizumi and Haake[8] studied the acid-catalysed hydrolysis of phosphinamides and suggested that the site of protonation of the substrates is important as it determined the reactivity of the protonated species. They proposed that the phosphinamides (26) are labile in acidic solutions because N-protonation occurs to give an intermediate (27) which is attacked by water (the nucleophile) in the second step of the reaction (Eq. 12).

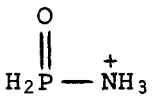


(26) (27) (12)

Molecular orbital calculations have been carried out on phosphinamide, $H_2P(O)NH_2$, and its protonated forms. The computed total energies indicated clearly that the O-protonated form (28) has greater thermodynamic stability than the N-protonated structure (29).[9]

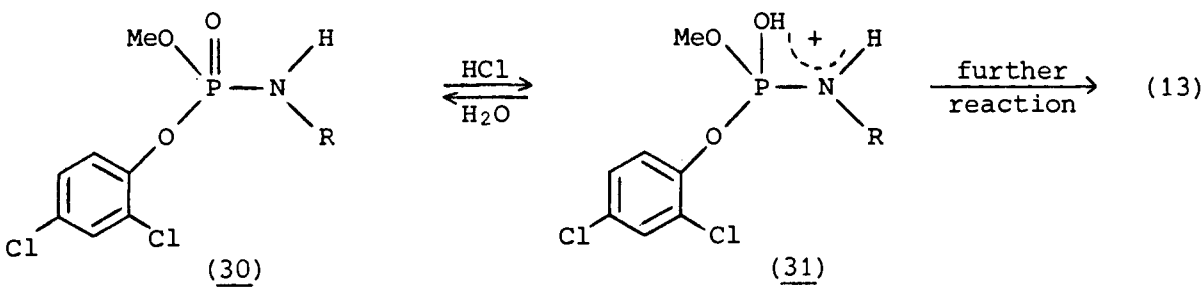


(28)



(29)

Garrison and Boozer[36] studied the hydrolysis of a series of 2,4-dichlorophenyl methyl N-alkylphosphoramidates (30) in the presence of HCl and concluded that reaction occurred *via* initial formation of the O-protonated form (31) (Eq. 13).

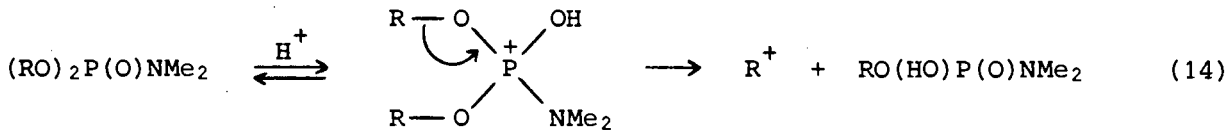


(30) (31)

R = alkyl group

The X-ray crystal structure analysis of protonated phenyl-(t-butyl)-phosphinamide, $[Ph(Bu^t)P(O)NH_2]_2.HCl$, showed that the conjugate acid corresponds to the O-protonated form.[10]

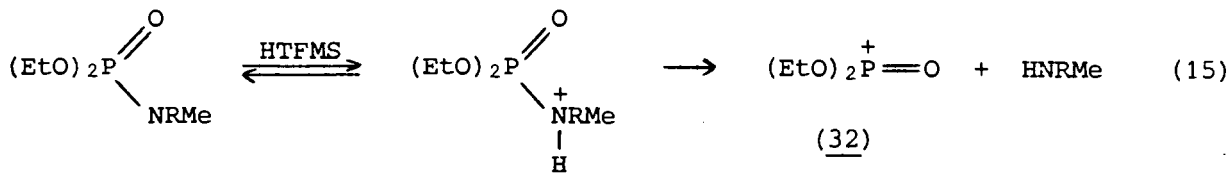
It has been shown that the P-N bond of $(RO)_2P(O)NMe_2$ is stable in anhydrous trifluoromethanesulphonic acid. O-dealkylation *via* an O-protonated intermediate occurred at a slow rate (Eq. 14); the rate of dealkylation was dependent on the protonation equilibrium.[11]



R = Me, Et, Pr^i

A great variation was observed in the rates of demethylation of $(MeO)_2P(O)X$; X = F, Cl, OMe, NMe_2. It was suggested that the reaction may involve both the monoprotonated form, $(MeO)_2P(OH)X^+$, and the diprotonated species, $(MeO)_2P(OH)XH^{2+}$, as reactive intermediates; the second protonation would depend on the nature of X.

In the present investigation of the acid-base behaviour of phosphoramidates of the general formula $(EtO)_2P(O)NRMe$ (11) an approach[12] was followed in which the difference between the ^1H n.m.r. chemical shifts of the α- and β-protons of (11) was used to establish the site of protonation of these compounds in anhydrous trifluoromethanesulphonic acid, HTFMS. This acid was chosen as it is one of the strongest acids known[37] and is a medium in which complete protonation of (11) would occur. The phosphoramidates are stable in HTFMS since the conjugate base, $CF_3SO_3^-$, is a very weak nucleophile and will not attack the protonated phosphoramidate *via* an S_N2 displacement at phosphorus.[11] Reaction *via* an S_N1 pathway is also unlikely as the phosphorylium ion (32) would be very unstable (Eq. 15).[38]



Aqueous acidic media are not suitable for the investigation of the acid-base behaviour of the phosphoramidates as the substrates are very labile under these conditions and P-N bond cleavage occurs rapidly.[36]

As the n.m.r. method used in this study depends on the position of the signals and not on their intensity, chemical reactions (unless they are fast) do not interfere, provided that signals from the products do not mask those of the starting material. Solvent effects are also minimised when using chemical shift differences as a probe of protonation behaviour as all atoms would be in approximately the same environment.

It was assumed that protonation of the phosphoramidates (11) would affect the chemical shifts of the β-methyl hydrogens of the ethoxy groups much less than those of the α-hydrogens of the ethoxy and N-methyl groups (Eq. 16).

$$\underset{\beta\ \alpha\qquad\qquad\alpha}{(CH_3CH_2O)_2P(O)NRCH_3} \quad \underset{}{\overset{H^+}{\rightleftharpoons}} \quad (CH_3CH_2O)_2\overset{+}{P}(OH)NRCH_3 \qquad (16)$$

(11) (12)

In the case of O-protonation (12) the positive charge of the quasiphosphonium ion formed should affect the chemical shifts of the O-methylene and N-methyl hydrogens (relative to the β-methyl group) to approximately the same degree. It must be noted that although in ions such as (12) there is a significant $p_\pi - d_\pi$ back-donation effect associated with the oxygen atom,[39] the charge remains symmetrically located with respect to the O- and N-α-hydrogens as shown below.

$$(CH_3CH_2O)_2\overset{OH}{\overset{|}{\underset{+}{P}}}NRCH_3 \quad \longleftrightarrow \quad (CH_3CH_2O)_2\overset{+OH}{\overset{\|}{P}}NRCH_3$$

(12)

N-protonation as in structure (13), should result in a much greater deshielding of the N-methyl hydrogens relative to those of the methylene group.

$$(CH_3CH_2O)_2P(O)\overset{+}{N}HRCH_3$$

(13)

The formation of complexes from the reaction of phosphoramidates with Lewis acids provides an alternate method of examining their acid-base behaviour. Phosphoryl compounds behave as strong oxygen bases towards Lewis acids.[13] As the phosphoryl oxygen atom acts as a donor centre, shielding effects[14] parallel to those operating in (12) can be investigated by studying the complexes (14) formed by reaction of the phosphoramidates (11) with titanium(IV) chloride (Eq. 17).

$$\underset{(11)}{(EtO)_2P(O)NRMe} \quad \underset{}{\overset{TiCl_4}{\rightleftharpoons}} \quad \underset{(14)}{(EtO)_2\overset{+}{P}(OTiCl_4)^-NRMe} \qquad (17)$$

The magnitude of the change in shielding parameters of the α- and β-hydrogens of the ethoxy-groups on converting the substrate into a quasiphosphonium ion [(11) → (12) or (11) → (14)] can be measured using triethyl phosphate (33) as a substrate (Eq. 18).

$$\underset{(34)}{(EtO)_3\overset{+}{P}-OH} \quad \overset{H^+}{\rightleftharpoons} \quad \underset{(33)}{(EtO)_3P=O} \quad \overset{TiCl_4}{\rightleftharpoons} \quad \underset{(35)}{(EtO)_3\overset{+}{P}-OTiCl_4^-} \qquad (18)$$

In triethylphosphate (33) only the phosphoryl oxygen is available as a donor atom. The phosphoryl group is more basic than the ester function owing to the contribution of the dipolar structure shown below.

$$\underset{(33)}{(EtO)_3P=O} \quad \longleftrightarrow \quad (EtO)_2\overset{+}{P}-\bar{O}$$

2.2 RESULTS AND DISCUSSION

Deshielding effects (relative to the chemical shifts of the neutral precursors) are given in Table 1. ^1H n.m.r. spectra indicating medium-induced shifts for $(EtO)_3P=O$ (33) are shown in Figure 1.

Table 1 Deshielding effects (in Hz) of complexation and protonation of phosphoryl compounds

	$\Delta(\beta\text{-Me}/OCH_2)$	Deshielding effect	$\Delta(\beta\text{-Me}/NMe)$	Deshielding effect
$(EtO)_3PO$ (33)[a]	278.0	-	-	-
Ti^{IV} complex (35)[b]	299.0	21.0	-	-
Protonated form (34)[c]	303.0	25.0	-	-
$(EtO)_2P(O)NMe_2$ (11a)[a]	271.0	-	137.5	-
Ti^{IV} complex[b]	295.5	24.5	144.0	6.5
Protonated form[c]	315.5	44.5	166.0	28.5
$(EtO)_2P(O)NMePh$ (11b)[a]	279.5	-	192.5	-
Ti^{IV} complex[b]	304.0	24.5	193.5	1.0
Protonated form[c]	308.0	28.5	216.5	24.0

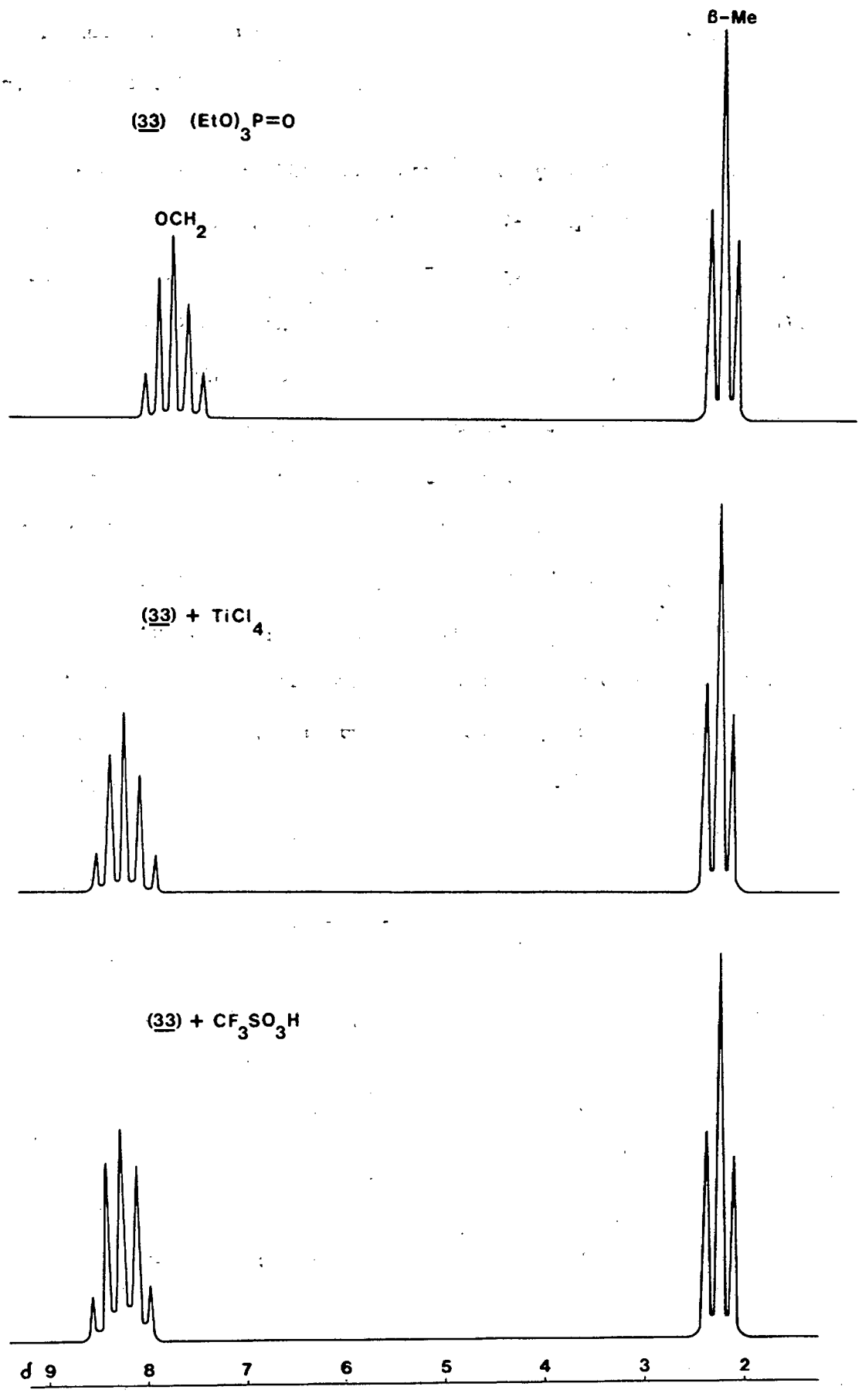
a Solution (5%) in $CDCl_3$

b Solution (5%) in $CDCl_3$ with three equivalents of $TiCl_4$

c Solution (5%) in HTFMS

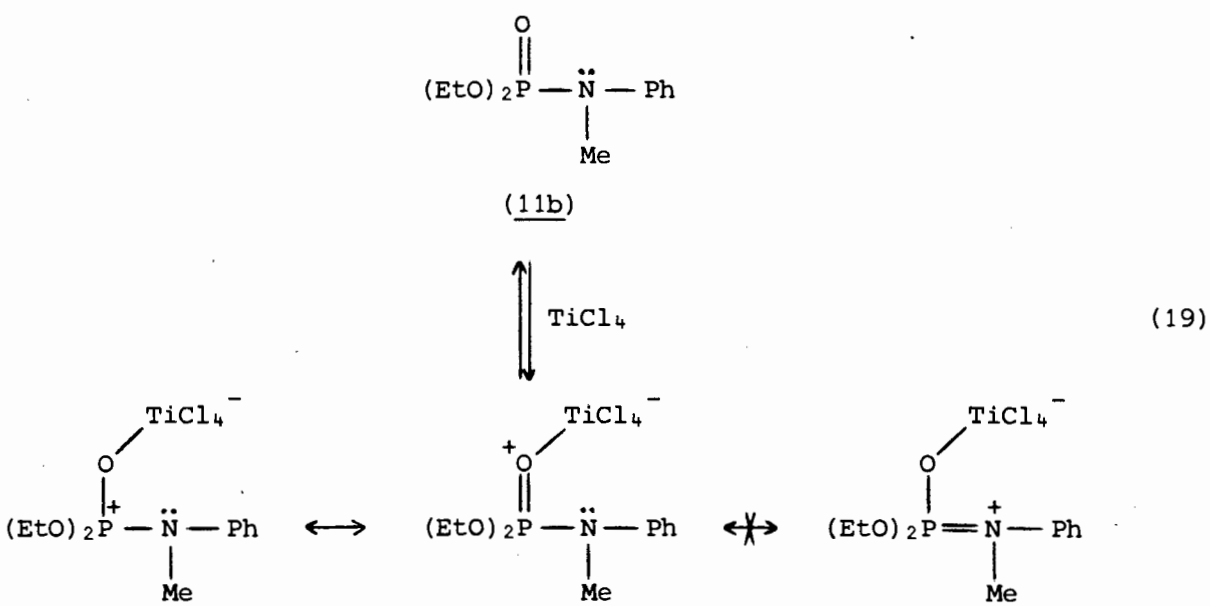
In the investigation of the complexation of (11) and (33) with $TiCl_4$ a three-fold excess of the Lewis acid was used. It is known that $TiCl_4$ forms 1:1 and 1:2 adducts with a variety of organophosphorus compounds containing the phosphoryl group. The shielding parameters of a series of phosphate esters

Figure 1 Medium effects on (33)



and phosphoramidates in the presence of $TiCl_4$ was investigated by ^{13}C n.m.r.[14] Constant values of chemical shifts were obtained at a three- to five-fold excess of Lewis acid indicating that under these conditions the complexation process (Eq. 17) is complete.

Both complexation with titanium(IV) and protonation by HTFMS result in considerable shifts to lower field of the O-methylene and N-methyl resonances relative to those of the β-methyl group. For $(EtO)_3P=O$ (33) the similarity in deshielding effects, (23 ± 2 Hz), on the O-methylene protons, demonstrates the similarity of charge distribution in $(EtO)_3\overset{+}{P}-OTiCl_4^-$ (35) and $(EtO)_3\overset{+}{P}-OH$ (34). Similar values of the deshielding effects on the O-methylene groups (24.5 Hz) are observed for the titanium(IV) complexes derived from phosphoramidates $(EtO)_2P(O)NMe_2$ (11a) and $(EtO)_2P(O)NMePh$ (11b), together with much smaller deshielding effects on the N-methyl groups (6.5 and 1.0 Hz respectively). This low response of the N-methyl group illustrates the previously reported reluctance of the nitrogen atom to donate its non-bonding electrons into the neighbouring phosphoryl centre, particularly when they are already involved in conjugative reactions with an aromatic ring (Eq. 19).[14]



(11b)

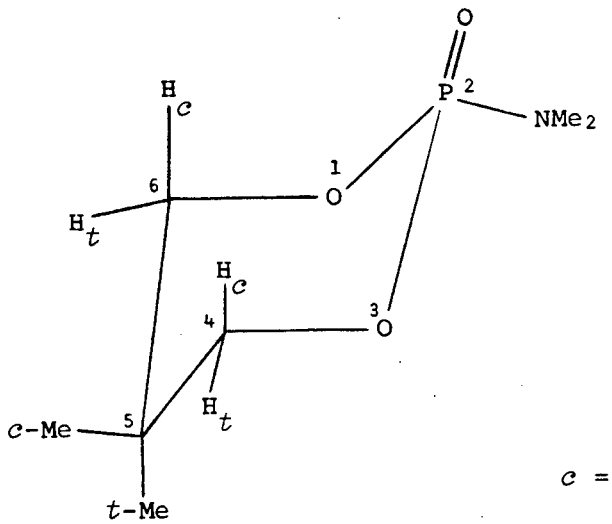
(19)

All substrates are stable enough in HTFMS to allow the recording of their n.m.r. spectra. Such a powerfully acidic medium has a profound effect on the chemical shifts of the hydrogen atoms close to the phosphoramidate function. For (11a) and (11b), the deshielding effects on the O-methylene group increased by 20 and 4 Hz respectively, as compared with those observed with titanium(IV) chloride. Even greater increases (22 - 23 Hz) were measured for the N-methyl resonance. For triethyl phosphate (33), complexation with titanium(IV) and protonation by HTFMS had a similar deshielding effect on the O-methylene group. Since, in HTFMS, both types of α-hydrogens of the phosphoramidates (11a) and (11b) are very strongly deshielded, it was concluded that in this medium phosphoramidates exist, at least partly, as doubly (O/N)-protonated conjugate acids (36) (See Eq. 20).

$$\underset{(11)}{(EtO)_2P(O)NRMe} \xrightleftharpoons{HTFMS} \underset{(12)}{(EtO)_2\overset{+}{P}(OH)NRMe} \xrightleftharpoons{HTFMS} \underset{(36)}{(EtO)_2\overset{+}{P}(OH)\overset{+}{N}HRMe} \qquad (20)$$

If the first (oxygen) protonation is not followed by significant back-donation of the nitrogen lone pair (as indicated by weak deshielding of the N-methyl group upon complexation), then a second protonation seems likely in view of the very high acidity of anhydrous HTFMS.[37]

The described approach is based on an assumption that the chemical shifts of the β-methyl groups are not affected significantly by changes in the electron density of the $\rangle P(O)N\langle$ function; thus they can be taken as true internal standards. This assumption was verified by examining the cyclic phosphoramidate, 5,5-dimethyl-2-dimethylamino-1,3,2-dioxaphosphorinan-2-one (37).

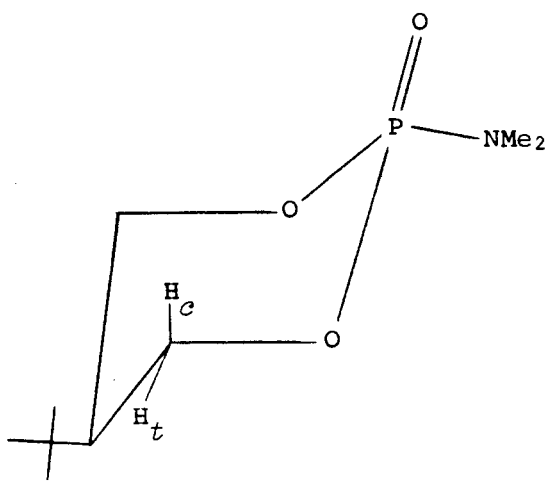


c = *cis* to P = O

t = *trans* to P = O

(37)

The conformation of (37) is represented best by the single chair-form isomer shown. Bentrude and Tan[40] examined the conformation of a series of saturated phosphorus heterocycles such as (38) by ^{1}H n.m.r.



(38)

The large value of J_{H_tP} (21.37 Hz) in (38) was interpreted as evidence for the equitorial orientation of the Me_2N group. J_{H_cP} was found to be 2.34 Hz. For (37) J_{H_cP} is 4.5 Hz and J_{H_tP} is 20 Hz. The parameters J_{H_cP} and J_{H_tP}

for (37) and (38) are similar to those found in other 2-oxo and 2-thio-1,3,2-dioxaphosphorinanes thought to exist in a single chair conformation. The relative shifts of the *cis* and *trans* protons in (37) and (38) *i.e.* $\delta_{cis} > \delta_{trans}$; are also consistent with the assignment of a single conformational isomer.[40]

In (37), changes in shielding parameters of the O-methylene and N-methyl hydrogens could be measured relative to those of the hydrogens of the 5-methyl groups, *i.e.* bonded to the carbon atoms γ with respect to the phosphoramidate function. The structure of (37) also allows a more detailed examination of the effects of protonation and complexation on shielding parameters within the molecular framework. Changes in chemical shifts of the O-methylene group could be measured independently for the hydrogen atoms *cis* (H_c) and *trans* (H_t) to the phosphoryl oxygen. The changes in the chemical shift differences between the H_c and H_t resonances and between the resonances of the *cis* (*c*-Me) and *trans* (*t*-Me) 5-methyl groups could also be determined. Finally, as an additional check, all shifts could be related to both (*cis* and *trans*) 5-methyl groups as internal standards. Results obtained for (37) are presented in Table 2. ^{1}H n.m.r. spectra indicating medium-induced shifts for (37) are shown in Figure 2.

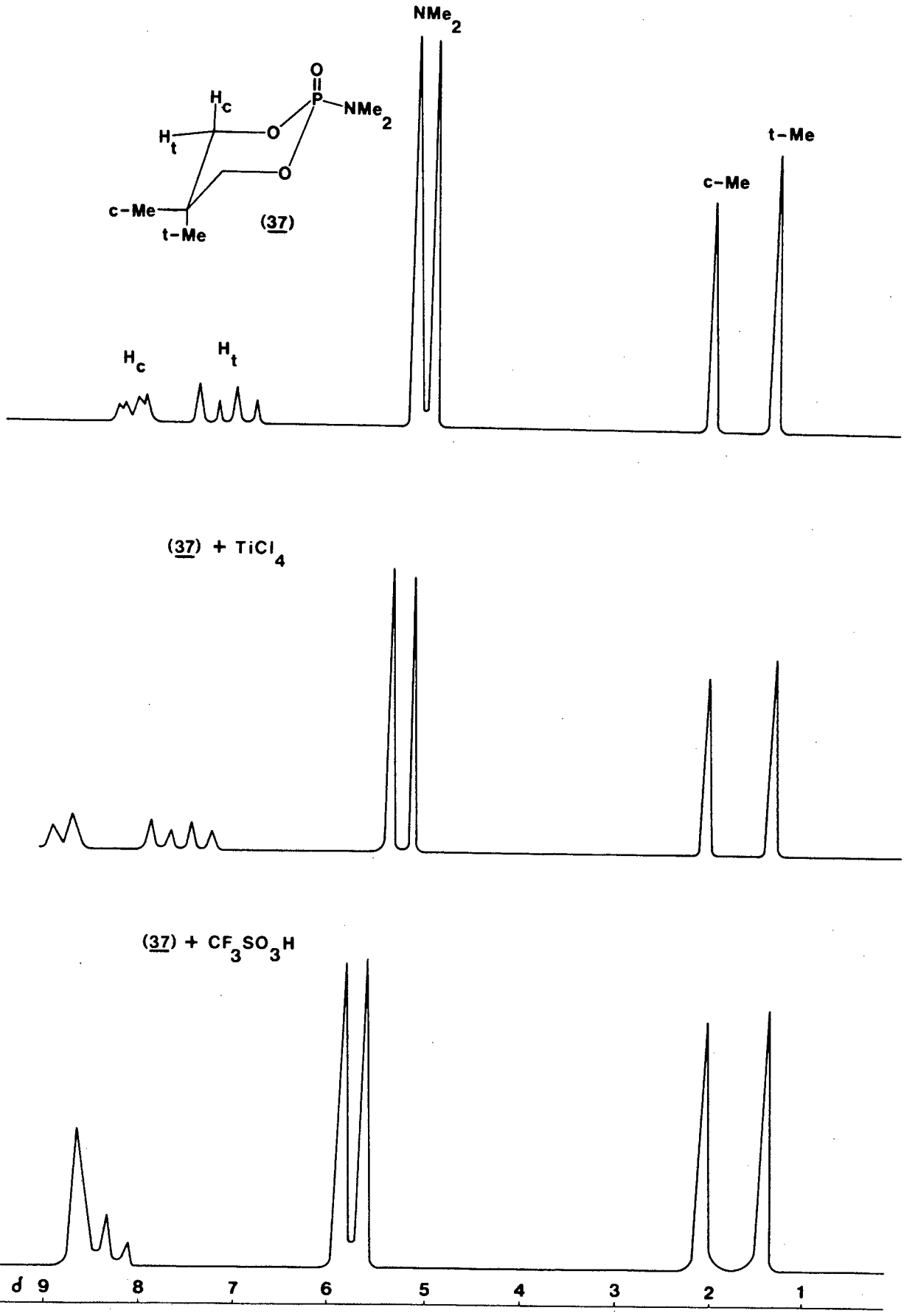
The chemical shift data in Table 2 are in excellent agreement with the model for (37) of oxygen complexation by titanium(IV) (39) and extensive O/N-diprotonation by HTFMS (40) (see Eq. 21).

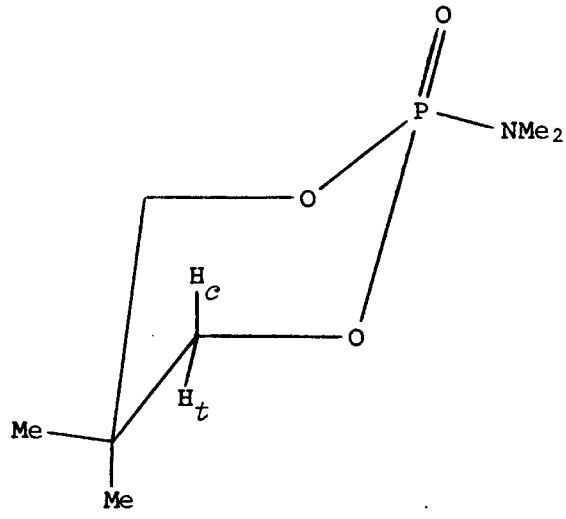
Table 2 Deshielding effects (in Hz) of complexation and protonation of 5,5-dimethyl-2-dimethylamino-1,3,2-dioxaphosphorinan-2-one (37)[a].

	Relative to the *c*-Me group			Relative to the *t*-Me group				
Medium	$\Delta(c\text{-Me}/H_c)$	$\Delta(c\text{-Me}/H_t)$	$\Delta(c\text{-Me/NMe})$	$\Delta(t\text{-Me}/H_c)$	$\Delta(t\text{-Me}/H_t)$	$\Delta(t\text{-Me/NMe})$	$\Delta(H_c/H_t)$	$\Delta(c\text{-Me}/t\text{-Me})$
$CDCl_3$	307.0	255.0	152.0	341.0	289.0	189.0	52.8	34.0
$CDCl_3 - TiCl_4$	341.0	278.0	161.5	376.0	313.0	196.5	62.5	35.0
Deshielding effect	34.0	23.0	9.5	35.0	24.0	7.5	9.7	1.0
HTFMS	330.0	320.0	184.0	362.5	352.5	217.0	10.0	33.0
Deshielding effect	23.0	65.0	32.5	21.5	63.5	28.0	-42.8	-1.0

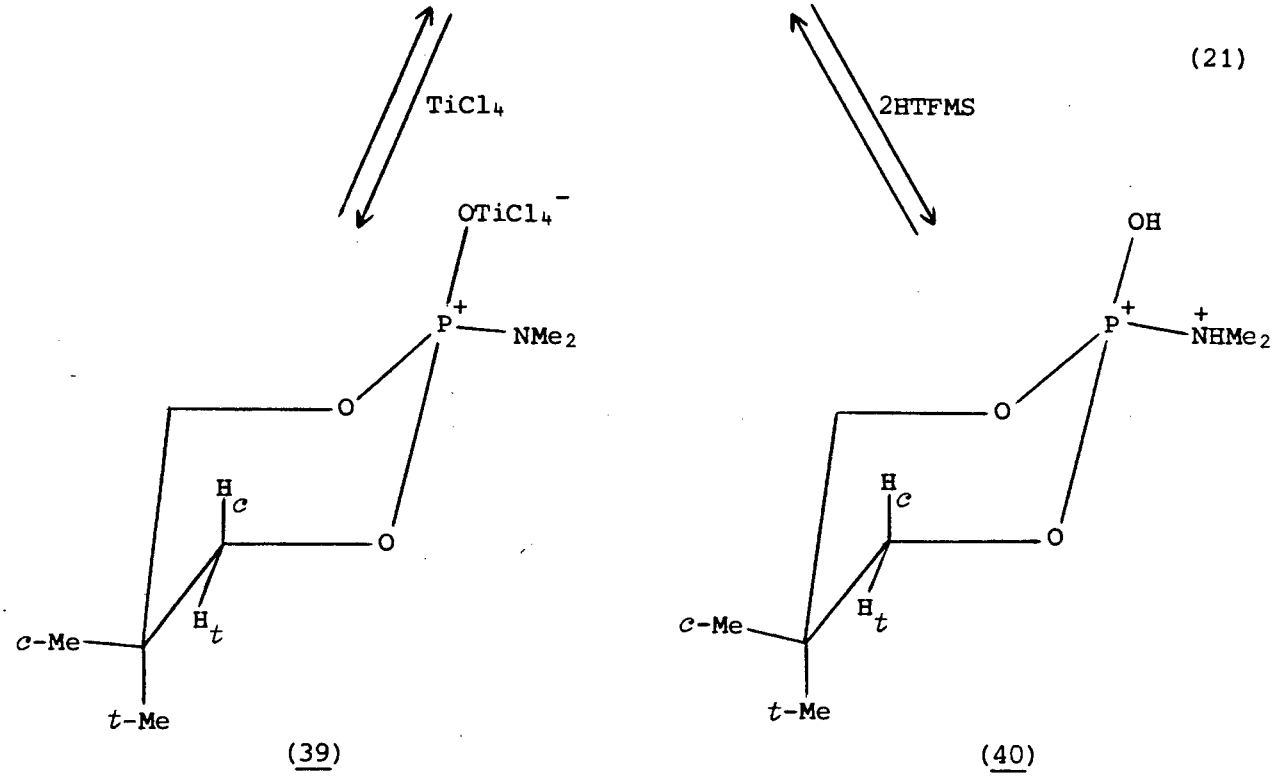
[a] Experimental conditions as given in Table 1.

Figure 2 Medium effects on (37)





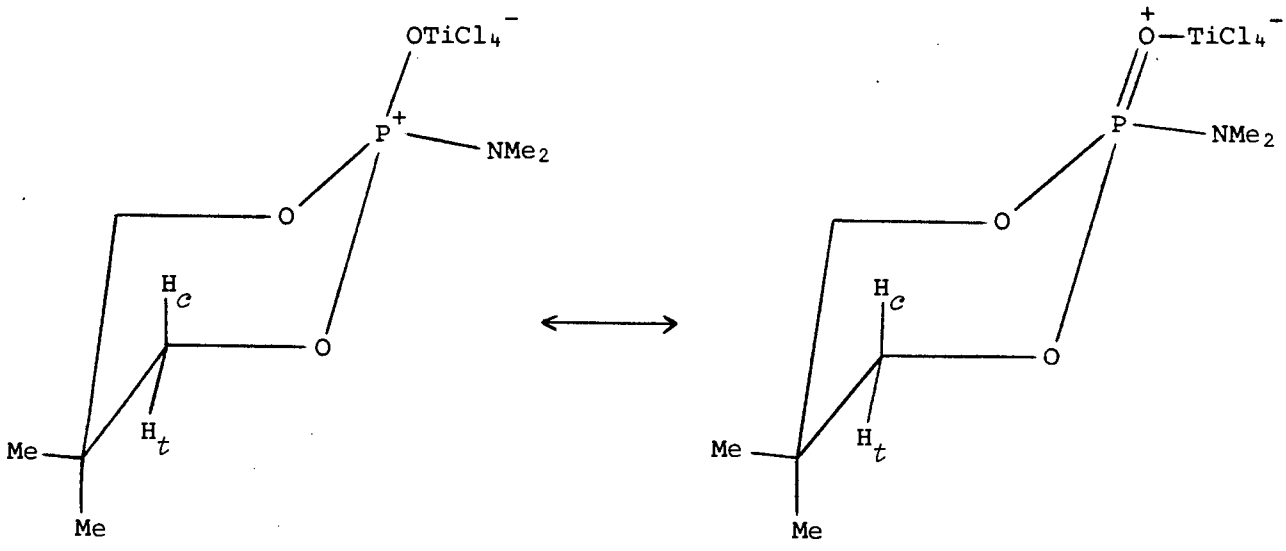
(37)



(21)

(39) (40)

Complexation according to (39) results in a stronger deshielding of the *cis*-hydrogen atoms, H_c, (34 - 35 Hz) than those of the *trans*-hydrogen atoms, H_t, (23 - 24 Hz) as H_c is closer to the phosphoryl oxygen atom than H_t. This indicates the development of a partial positive charge at the exocyclic oxygen atom according to the phosphonium-oxonium resonance model of the $[X_3P - OZ]^+$ (Z = H, $TiCl_4$) system[41] as shown below.



(39)

The increase in the electronegativity of the phosphoryl oxygen atom is also evidenced by a greater separation between the H_c and H_t signals (9.7 Hz) and the *c*-Me and *t*-Me signals (1.0 Hz) relative to the neutral substrate.

The effect of HTFMS on the n.m.r. spectrum of (37) parallels that observed for $(EtO)_2P(O)NMe_2$ (11a). The average deshielding of the O-methylene protons of (37) on protonation is 43.3 Hz* compared with 44.5 Hz for the protonated form of (11a). The second positive charge is, however, developed at the nitrogen atom and thus the signals of H_t (*cis* to the dimethylamino-group) are shifted to lower field much more strongly than those of H_c (*trans* to the Me_2N group). The average deshielding of the N-methyl protons of (40) is 30 Hz, close to the value of 28.5 Hz observed for (11a) in HTFMS. The presence of a highly localised charge at nitrogen in (40) has a strong effect on the difference in shielding of hydrogens H_c and H_t, $\Delta(H_c/H_t)$. This difference is decreased in

*Average deshielding of the O-methylene protons H_c and H_t relative to the *cis* and *trans* methyl groups *viz.* $\Delta(c\text{-Me}/H_c)$ = 23 Hz, $\Delta(c\text{-Me}/H_t)$ = 65 Hz, $\Delta(t\text{-Me}/H_c)$ = 21.5 Hz and $\Delta(t\text{-Me}/H_t)$ = 63.5 Hz

HTFMS to *ca.* 10 Hz compared with $\Delta(H_c/H_t)$ 52.8 Hz in $CDCl_3$ and 62.5 Hz in $CDCl_3$ - $TiCl_4$. The difference in chemical shifts of the *cis* and *trans* methyl groups, $\Delta(c\text{-Me}/t\text{-Me})$, is also decreased slightly.

The results discussed above indicate that in the amide molecule $X(Y)P(O)NR_2$ (8) protonation of the phosphoryl oxygen atom followed by N-protonation can occur under the appropriate conditions. It is difficult to predict the concentration of the diprotonated form (41) in media of lower acidity than anhydrous HTFMS.

$$X(Y)\overset{+}{P}(OH)\overset{+}{N}HR_2$$

(41)

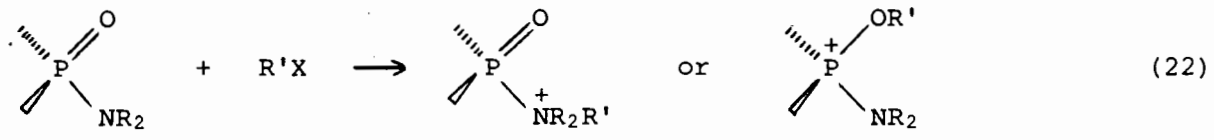
The intermediate (41) should be highly reactive towards nucleophilic attack and subsequent P-N bond cleavage; thus (41) should offer a convenient pathway in the acid-catalysed reactions of phosphoramidates. The extremely electrophilic phosphorus atom in (41) would allow facile attack even by weak nucleophiles.

CHAPTER THREE

NUCLEOPHILICITY OF THE PHOSPHORAMIDATE FUNCTION

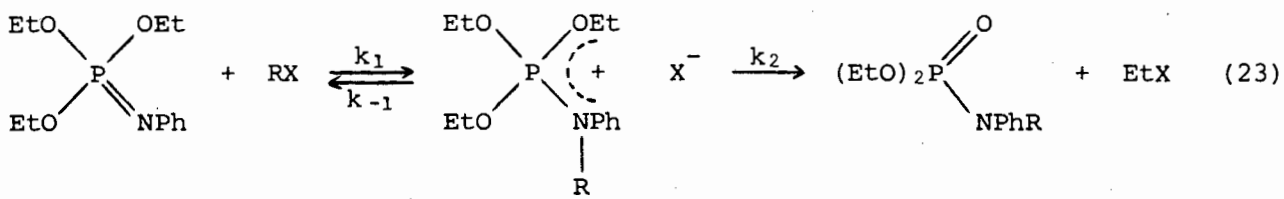
3.1 INTRODUCTION

The phosphoramidate function (42) can act as an ambident nucleophile and upon alkylation can give rise to products resulting from nucleophilic attack by the amide nitrogen atom or the phosphoryl oxygen atom (Eq. 22).



(42) (22)

The bimolecular alkylation reactions of organophosphorus substrates have been examined[15] and the nucleophilic reactivity of the nitrogen atom and the phosphoryl oxygen atom with respect to alkylating reagents has been studied for various phosphorimidates. The imidate-amidate rearrangement (43) → (44) in the presence of alkyl halides is best explained by an S_N2 process (Eq. 23).[15]

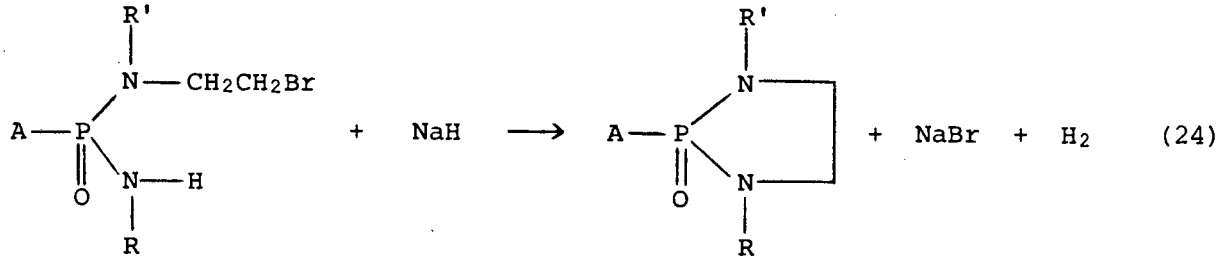


(43) (45) (44) (23)

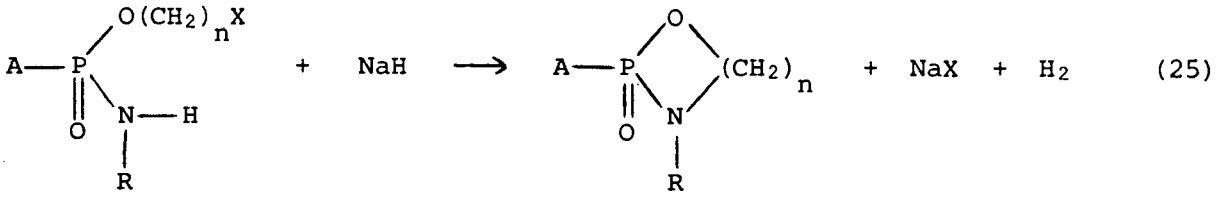
X = I, Br, Cl

Rate-limiting attack by the phosphorimidate (43) on the alkyl halide produces an ionic intermediate (45). This is followed by rapid removal of the O-ethyl group by the halide ion to give the phosphoramidate (44).

Intramolecular alkylation reactions of phosphoramidates have also been investigated. Thus Savignac[42] and co-workers have reported the reactions of some phosphoramidates in the presence of sodium hydride (Eq. 24 and 25).



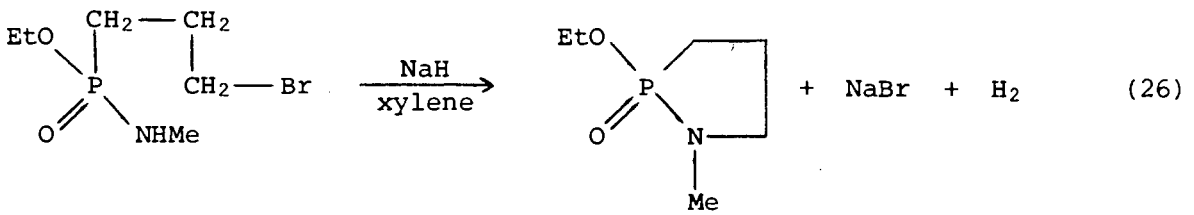
(24)



(25)

n = 2,3; X = Cl, Br; A = Et, Ph; R = alkyl group.

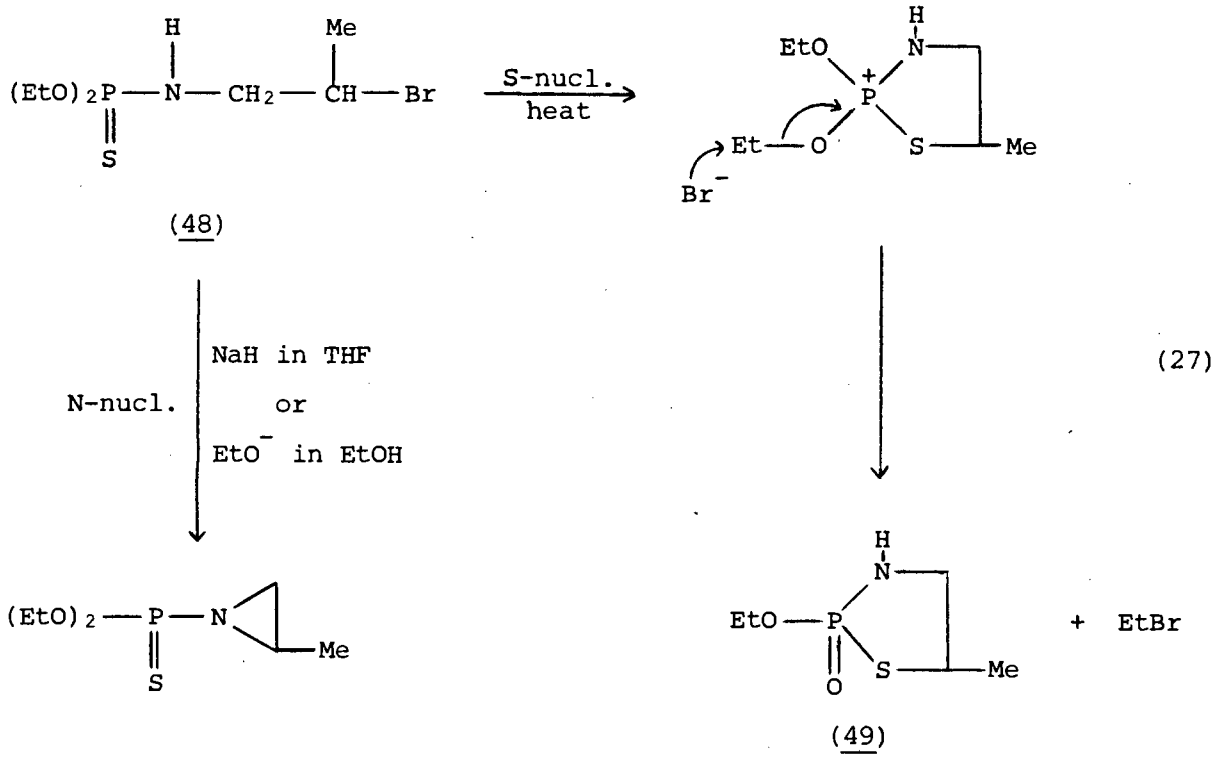
The phosphoramidate (46) reacts with NaH in xylene to give (47) (Eq. 26).[43]



(26)

(46) (47)

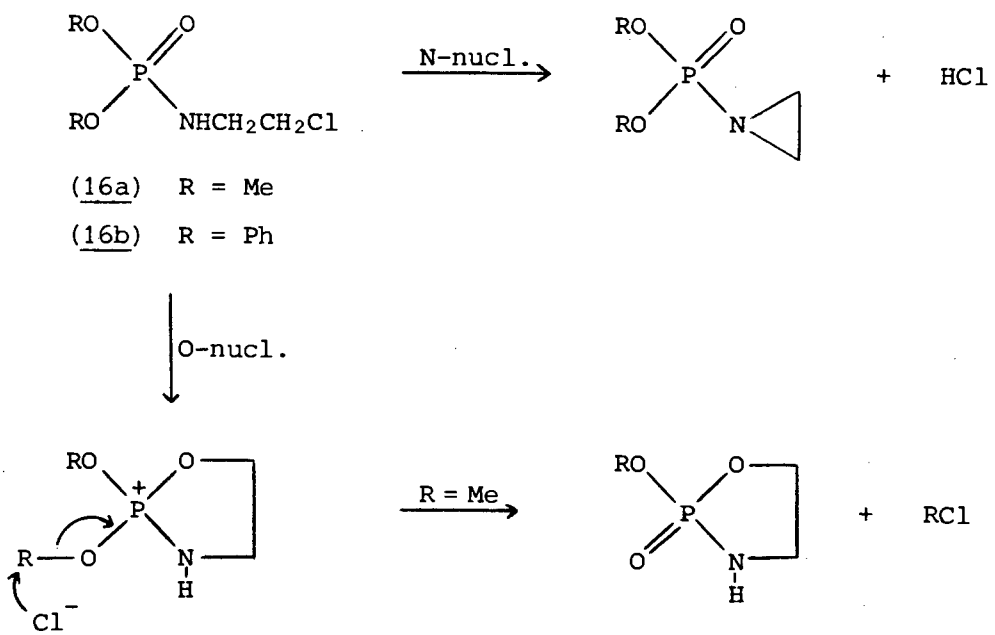
The phosphorothioamidate (48) is also an ambident nucleophile capable of nucleophilic reactivity *via* the nitrogen or sulphur atoms. It undergoes ring closure on heating or treatment with a base (Eq. 27).[44]



(27)

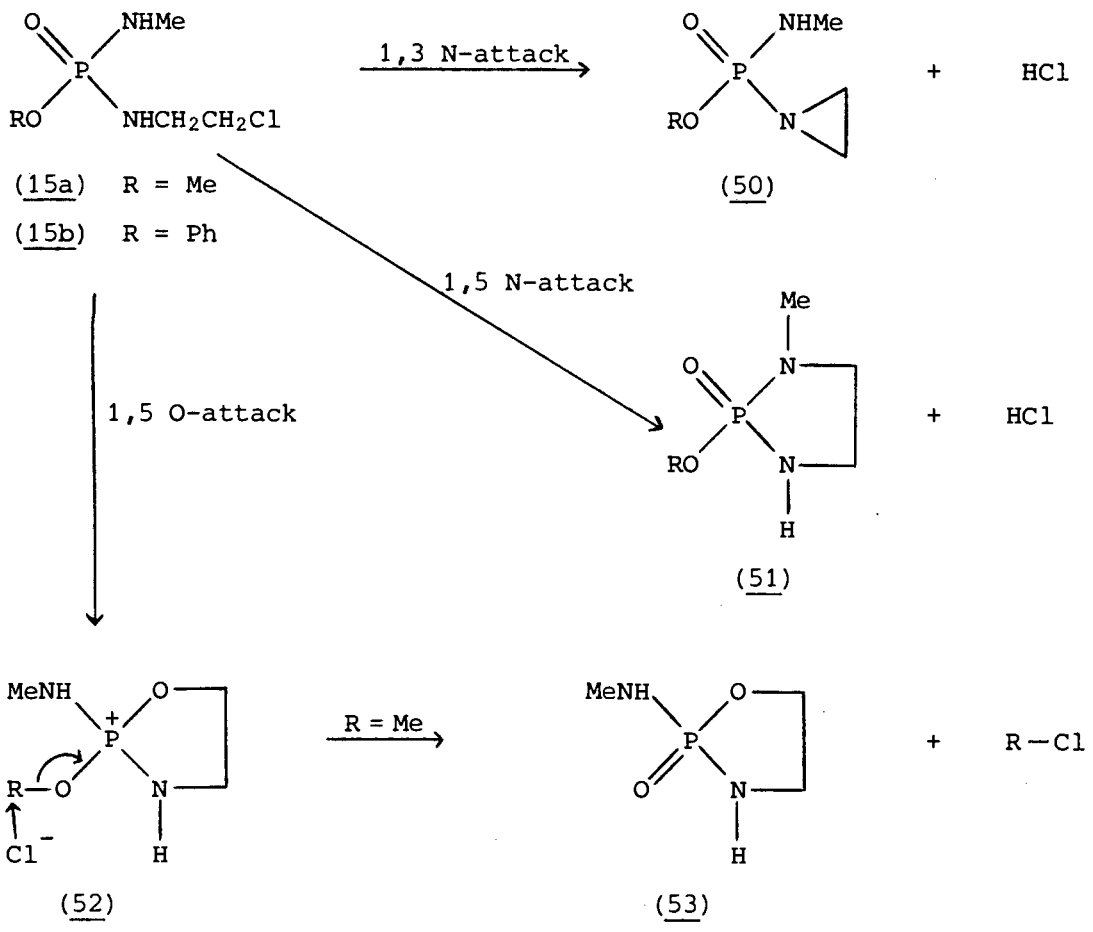
The formation of (49) occurs in two steps and is analogous to the Michaelis-Arbuzov reaction.[45]

The N-(β-chloroethyl)phosphoramidates (16) can react *via* two main pathways as shown in Scheme 2.



Scheme 2

The phosphorodiamidates (15) have three potential nucleophilic centres and could in principle react as shown in Scheme 3.



Scheme 3

Intermolecular reactions between phosphoramidates and alkyl halides are well-known;[15] in this work the intramolecular reactions of the phosphoramidates (15) and (16) as well as related compounds were investigated under various conditions in order to determine the preferred reaction pathway in these compounds.

3.2 RESULTS AND DISCUSSION

3.2.1 N-(β-HALOETHYL)PHOSPHORAMIDATES AND PHOSPHINAMIDATES

These compounds were synthesised from phosphorochloridates or phosphinic chlorides and β-chloroethylammonium chloride in ether in the presence of triethylamine as a base (Eq. 28).

$$X_2P(O)Cl + ClCH_2CH_2NH_2.HCl \xrightarrow[ether]{Et_3N} X_2P(O)NHCH_2CH_2Cl \qquad (28)$$

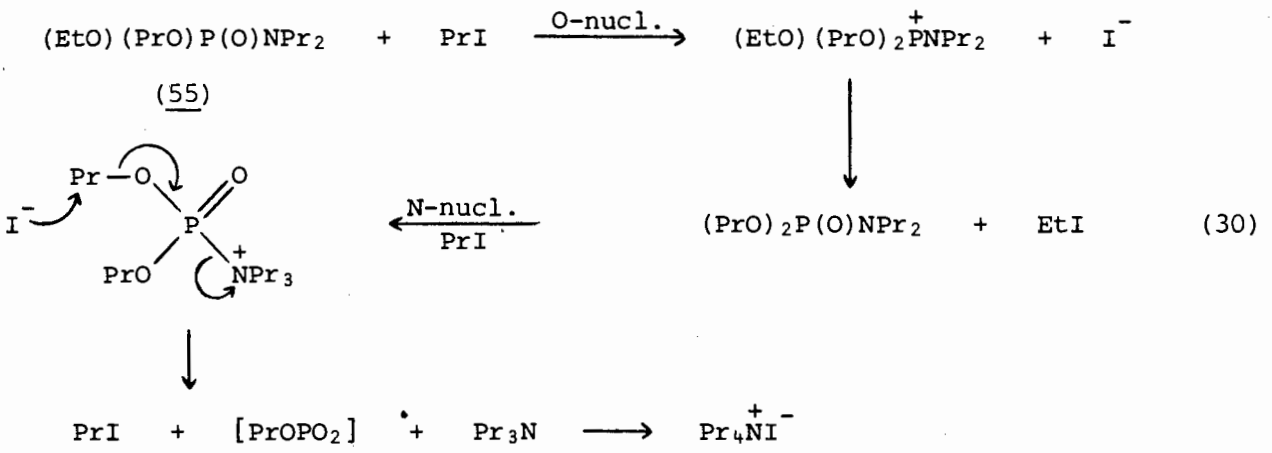
(16a) X = MeO
(16b) X = PhO
(16c) X = Et
(16d) X = Ph

Similarly $(MeO)_2P(O)NHCH_2CH_2Br$ (54) was prepared from dimethylphosphorochloridate and β-bromoethylammonium bromide (Eq. 29).

$$(MeO)_2P(O)Cl + BrCH_2CH_2NH_2.HBr \xrightarrow[ether]{Et_3N} (54) \qquad (29)$$

(16a), a high-boiling liquid, was purified by distillation. (16b) was obtained as a pure solid from the reaction mixture. (16d) was purified by recrystallisation. (16c) and (54) were very viscous oils which could not be distilled and they were purified by column chromatography. All compounds were stable and could be stored for several months without deterioration.

In intermolecular reactions between phosphoramidates and alkyl halides both the phosphoryl oxygen and amidate nitrogen atoms can act as nucleophiles. This has been demonstrated by the reaction of ethyl propyl N,N-dipropyl-phosphoramidate (55) with iodopropane (Eq. 30).[46]



The substrate (55) was heated under reflux for 96 hours with a five-fold excess of the alkylating agent, iodopropane.

In the present work the phosphoramidates (16a) and (54) were recovered unchanged after heating under reflux for 48 hours in a variety of solvents *viz.* deuteriochloroform, acetone and chlorobenzene. Thus systems having the nucleophile and electrophilic centre (β-carbon atom) within the same molecular framework do not undergo thermally-induced intramolecular alkylation reactions.

Refluxing $(MeO)_2P(O)NHCH_2CH_2Br$ (54) in benzene containing an equimolar quantity of pyridine resulted in a reaction in which pyridine acted as an external nucleophile with respect to the methyl group of (54) forming the corresponding N-methylpyridinium derivative (56) (Eq. 31).

$$(MeO)_2P(O)NHCH_2CH_2Br \xrightarrow[\text{benzene}]{C_5H_5N} {}^{-}O(MeO)P(O)NHCH_2CH_2Br.C_5H_5\overset{+}{N}Me \qquad (31)$$

(54) (56)

(56) was identified from its ^1H n.m.r. spectrum which showed the absence of substrate. The signals of the N-methylpyridinium cation were identical to those observed for an authentic sample of N-methylpyridinium iodide. The protons of the O-methyl group of (56) were shielded relative to those of the neutral precursor (54) due to the close proximity of the negative charge.

In this reaction pyridine did not enhance the internal nucleophilicity of the substrate by abstraction of the NH proton of (54) but acted as a nucleophile attacking the electrophilic centre at the saturated carbon atom of the methyl group.[47]

Displacement of the chlorine atom in $X_2P(O)NHCH_2CH_2Cl$ (16) can, however, be promoted in two ways. One involves an increase in the electrophilicity of the β-carbon atom by catalysis with silver ions; in the other the nucleophilicity of the $\rangle P(O)NH\langle$ group is increased by abstraction of the proton by a strong base (NaH or BuLi). For (16a), (16c) and (16d) both reactions proceeded smoothly with exclusive formation of the N-phosphorylated ethylenimine (22) (Eq. 32).

$$X_2P(O)NHCH_2CH_2Cl \xrightarrow[\text{or NaH in THF}]{Ag^+/OH^- \text{ in } H_2O} X_2P(O)N\triangle \qquad (32)$$

(16a,c,d) — or BuLi in THF

(22a) X = MeO
(22b) X = Et
(22c) X = Ph

Similar treatment of $(MeO)_2P(O)NHCH_2CH_2Br$ (Ag^+ or NaH) yielded (22a). In all reactions the N-phosphorylated ethylenimine (22) could be identified easily by ^1H n.m.r. owing to the characteristic high-field doublet [$\delta(CDCl_3) \sim 2.1$, $J_{H,P}$ 14 - 16 Hz] of the four equivalent protons of the ethylenimine ring (see Chapter 7.3).

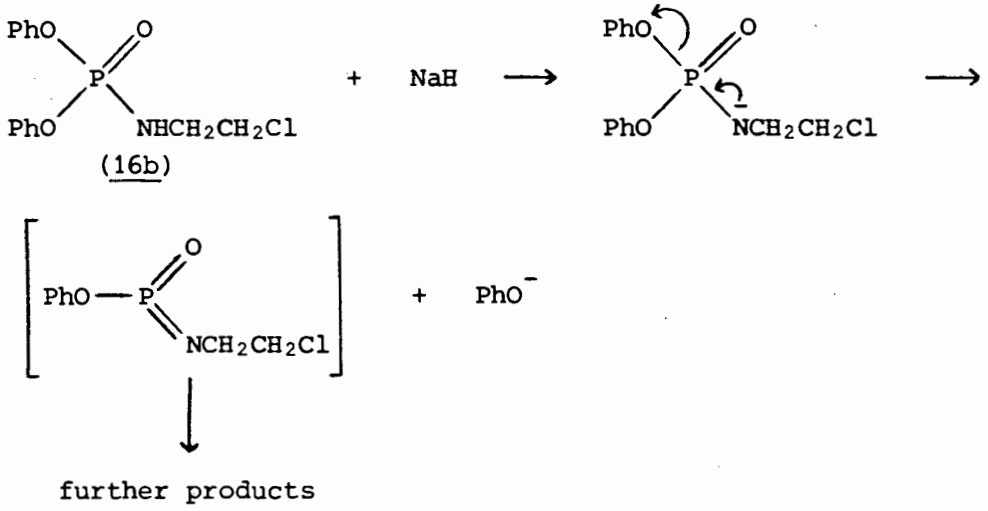
When $(PhO)_2P(O)NHCH_2CH_2Cl$ (16b) was treated under these conditions, however, low yields of the corresponding ethylenimine were obtained. It was suspected that the low yields were not due to difficulty of formation of the phosphorylated ethylenimine but rather to elimination of the phenoxide ion under the

basic conditions used in the reaction to form (22). $(PhO)_2P(O)NHMe$ (18Ba)* was used as a simple model compound in order to investigate possible expulsion of the phenoxide ion. Although it does not contain the β-chlorine atom it is a secondary amide and has two phenyl ester groups at phosphorus. Reaction of (18Ba) with NaH, acidification of the reaction mixture and subsequent treatment with bromine led to the isolation of 2,4,6-tribromophenol (Eq. 33).

$$(PhO)_2P(O)NHMe \;+\; NaH \xrightarrow[3.\ Br_2]{1.\ THF,\ 2\ hrs \;\; 2.\ 5\%\ H_2SO_4} C_6H_2Br_3OH \qquad (33)$$

(18Ba)

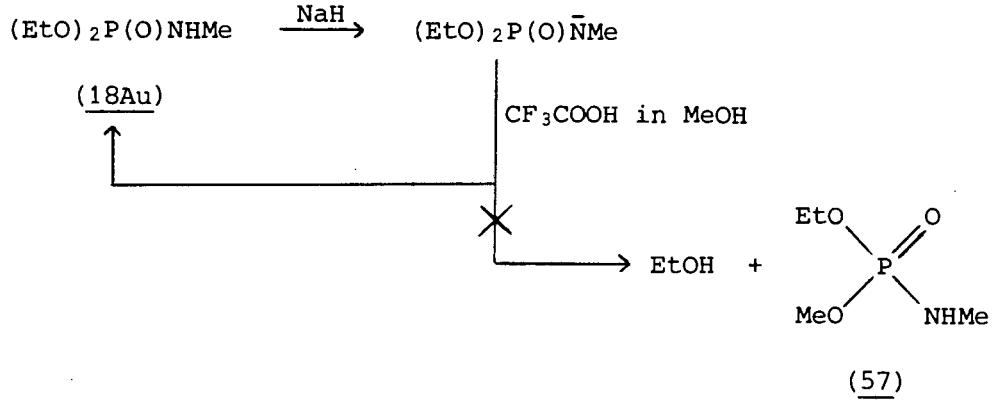
Treatment of $(PhO)_2P(O)NHCH_2CH_2Cl$ (16b) as described for (18Ba) also resulted in the isolation of 2,4,6-tribromophenol. Thus $(PhO)_2P(O)N$ cannot be prepared by the route used to form (22a,b,c) (see Eq. 32) due to elimination of the phenoxide ion which probably proceeds as shown in Eq. 34.



(34)

*This composite number is derived from the general formula $(RO)_2P(O)R'R''$ (18) (see Chapter 1); (18A), R = alkyl; (18B), R = Ph; R', R'' = H, alkyl, aryl. The letters a, b, c... refer to specific combinations of R' and R'' within the group of compounds having the same general formula (18A) or (18B) *e.g.* $(MeO)_2P(O)NHMe$ (18Aa), $(PhO)_2P(O)NHMe$ (18Ba) and $(EtO)_2P(O)NHMe$ (18Au).

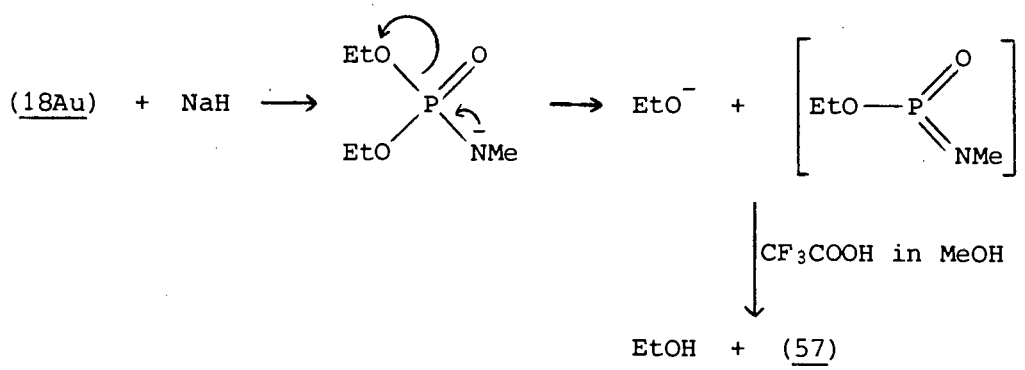
No elimination of ethoxide ion was observed when $(EtO)_2P(O)NHMe$ (18Au) was stirred for 2 hours at room temperature in THF containing NaH. The substrate was recovered unchanged after neutralisation of the reaction mixture with CF_3COOH. A mixture of (18Au) and NaH in THF heated under reflux for 1 hour and neutralised with trifluoroacetic acid in a large volume of methanol showed no incorporation of methanol to form the phosphoramidate (57) and the substrate was recovered unchanged (Eq. 35).



(35)

(57)

Incorporation of methanol to form (57) can only occur *via* unimolecular collapse of the conjugate base of (18Au) by the Elcb pathway shown in Eq. 36.

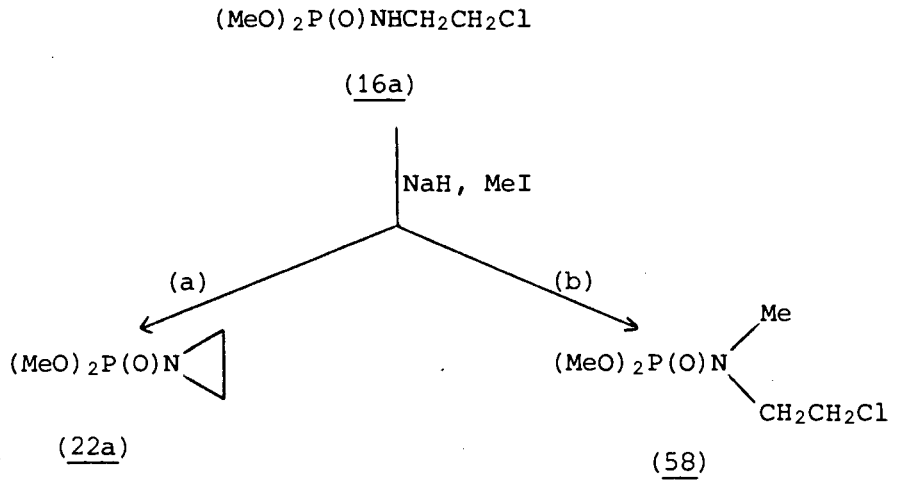


(36)

In aqueous alkaline solutions, however, secondary amides such as $(MeO)_2P(O)NHMe$ (18Aa) do release a methoxide ion, probably *via* a reaction analogous to Eq. 36. The kinetics of this reaction are discussed in Chapter 5.

3.2.2 INTRA- *vs.* INTERMOLECULAR ALKYLATION REACTIONS

There are two reaction pathways available when the phosphoramidate $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) is treated with NaH in the presence of an alkylating agent such as iodomethane, *viz.* an intramolecular displacement of the chloride ion to form the ethylenimine derivative (22a), or an intermolecular alkylation forming the N-methyl derivative (58) (Eq. 37).



(37)

$(MeO)_2P(O)NHMe$ (18Aa) was used as a simple model for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) to investigate the intermolecular reaction between phosphoramidates and alkyl halides in the presence of sodium hydride. When (18Aa) is treated with iodomethane and NaH it is converted into $(MeO)_2P(O)NMe_2$ (21) (Eq. 38).

$$(MeO)_2P(O)NHMe \quad (18Aa) \quad + \quad MeI \quad \xrightarrow[THF]{NaH} \quad (MeO)_2P(O)NMe_2 \quad (21) \qquad (38)$$

(21) was identical to the product synthesised from $(MeO)_2P(O)Cl$ and Me_2NH. (18Aa) did not react with MeI in the absence of NaH.

When $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) was heated under reflux for 2 hours with a five-fold excess of MeI the substrate was recovered unchanged. Addition of NaH yielded a mixture of (22a) and (58) which were formed as a result of intra-

and intermolecular displacement of the chloride ion, respectively (see Eq. 37). The mixture of products was identified by its ^{1}H n.m.r. spectrum which showed the absence of any substrate; (22a) by the characteristic high-field doublet of the ethylenimine group [δ ($CDCl_3$) 2.20, $J_{H,P}$ 16 Hz] as well as by addition of authentic material, and (58) by the doublet arising from the NMe group [δ ($CDCl_3$) 2.76 $J_{H,P}$ 10 Hz]. The chemical shift of this methyl group is very similar to δ 2.80 observed for NMe in $(MeO)_2P(O)NMe_2$ (21). The bimolecular reaction predominates when a five-fold excess of MeI is used and more than 90% of the N-methylated product (58) is obtained.

In order to compare the reactivity of (16a) towards intra- and intermolecular alkylation, equimolar quantities of (16a), MeI and NaH were reacted together in varying volumes of tetrahydrofuran and the results obtained are shown in Table 3.

Table 3. Relative ratios[1] of (58) and (22a) on treatment of (16a) with MeI and NaH.

[Substrates], *M*	(58) : (22a)
0.100	2.86 : 1
0.050	2.12 : 1
0.033	1.57 : 1

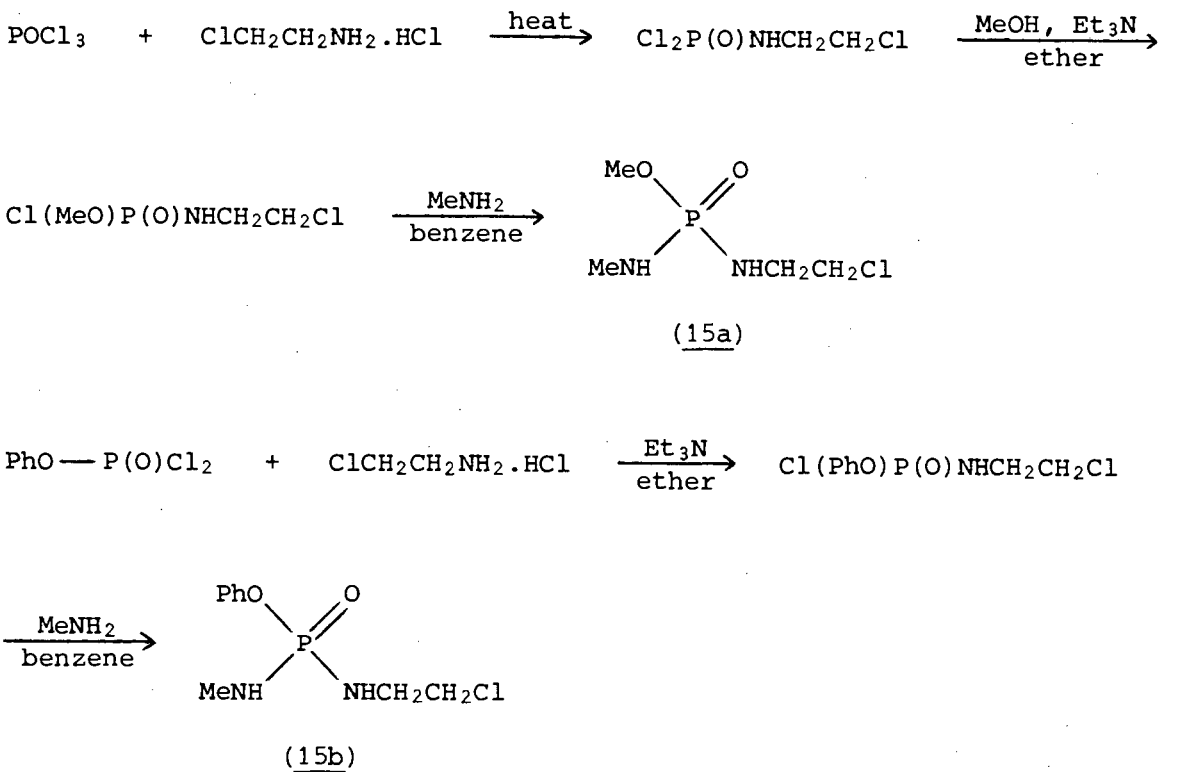
1. Ratios were determined from the integrated height of the NMe hydrogen resonance of (58) relative to the NC_2H_4 hydrogen resonance of (22a) statistically corrected to the number of hydrogen atoms present.

As expected the amount of product (58) formed by the bimolecular reaction of (16a) with MeI decreases as the solution is diluted. The rate of the bimolecular (S_N2) reaction, [Eq. 37, pathway (b)] decreases more on dilution than

the rate of the unimolecular reaction [pathway (a)]. The formation of the three-membered ring together with the bimolecular reaction with MeI shows the comparable reactivity of the conjugate base of (16a) towards intra- and intermolecular alkylation.

3.2.3 N-METHYL-N'-(β-CHLOROETHYL)PHOSPHORODIAMIDATES

These substrates were synthesised according to Scheme 4.

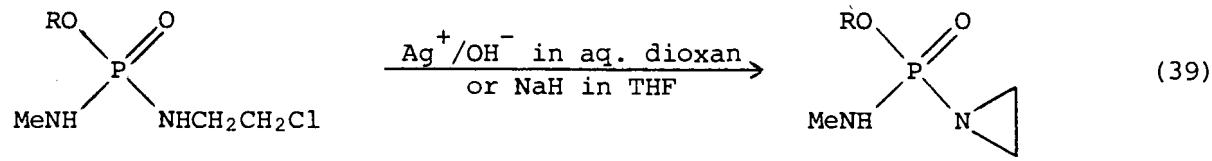


Scheme 4

Both products were very viscous oils which could not be distilled. (15a) and (15b) were purified by column chromatography and yields were low (39 - 45%). The diamidates were stable and could be stored for several months without deterioration.

The possible reaction pathways available to (15a,b) are outlined in Scheme 3 (Chapter 3.1). Electronic effects operating in the pathways leading to products (50) and (51) are to a first approximation the same and the product composition should directly reflect the preference of the substrate for the formation of a three- or five-membered cyclic derivative. For (15a) the presence of the O-methyl group should allow the quasiphosphonium intermediate (52) to demethylate to give (53) according to the usual Arbuzov-type reaction.[45]

Intramolecular substitution of the chloride ion could not be induced thermally for (15a) or (15b) but both electrophilic (Ag^+) or basic (NaH) catalysis resulted in the formation of the ethylenimine derivative (50) (Eq. 39).



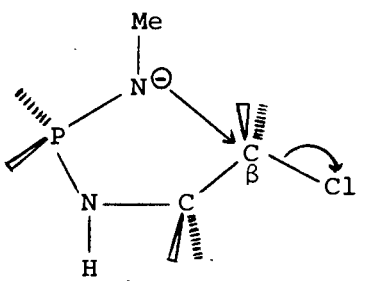
(15a,b) (39)

(50a) R = Me

(50b) R = Ph

Even though an excess of reagent was used and the reaction mixture was heated under reflux for up to 24 hours the product of the reaction shown in Eq. 39 was always a mixture containing unreacted starting material (15) and the N-phosphorylated ethylenimine (50). This was easily identified by the high-field doublet [δ ($CDCl_3$) $\sim$ 2.14, $J_{H,P}$ 14 - 16 Hz] of the ethylenimine substituent. Yields of (50) were estimated from the ratio of the protons of the ethylenimine ring relative to those of the NCH_2CH_2 moiety in (15) and were: (50a); 39% (Ag^+) and 45% (NaH), (50b); 70% (Ag^+) and 56% (NaH). (15b) has a phenyl ester group and when reacted with NaH it gave phenol as well as (50b). This parallels the behaviour of $(PhO)_2P(O)NHCH_2CH_2Cl$ (16b) which yielded phenol on treatment with NaH. Attempts to isolate and purify

(50b) by column chromatography were unsuccessful as the product decomposed and only phenol was isolated. The formation of the three-membered ring by intramolecular alkylation is the predominant reaction for (15). The formation of products having five-membered rings, *e.g.* (51) and (53), cannot be excluded but these were never identified or isolated. As discussed earlier in Chapter 3.2.2 $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) undergoes both intra- and intermolecular alkylation reactions when treated with NaH and MeI (see Eq. 37). The failure of the phosphorodiamidates (15) to form the five-membered cyclic products (51, Scheme 3) when treated with NaH suggests that the conformation (59) necessary to achieve intramolecular ring closure is not favourable.

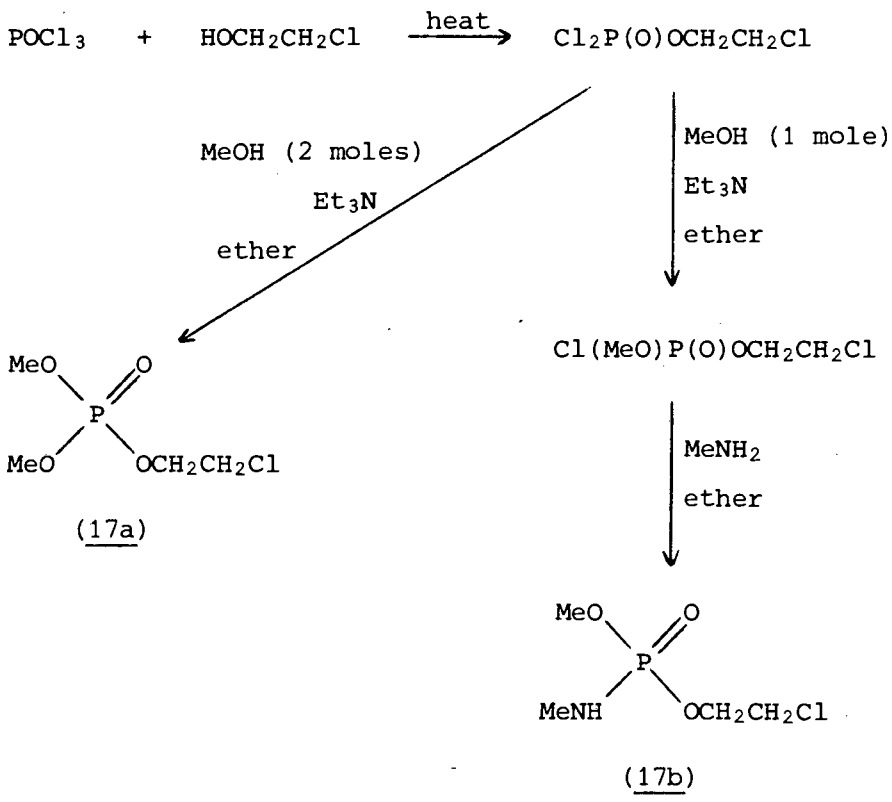


(59)

3.2.4 O-(β-CHLOROETHYL)PHOSPHATES AND PHOSPHORAMIDATES

These compounds were synthesised according to Scheme 5.

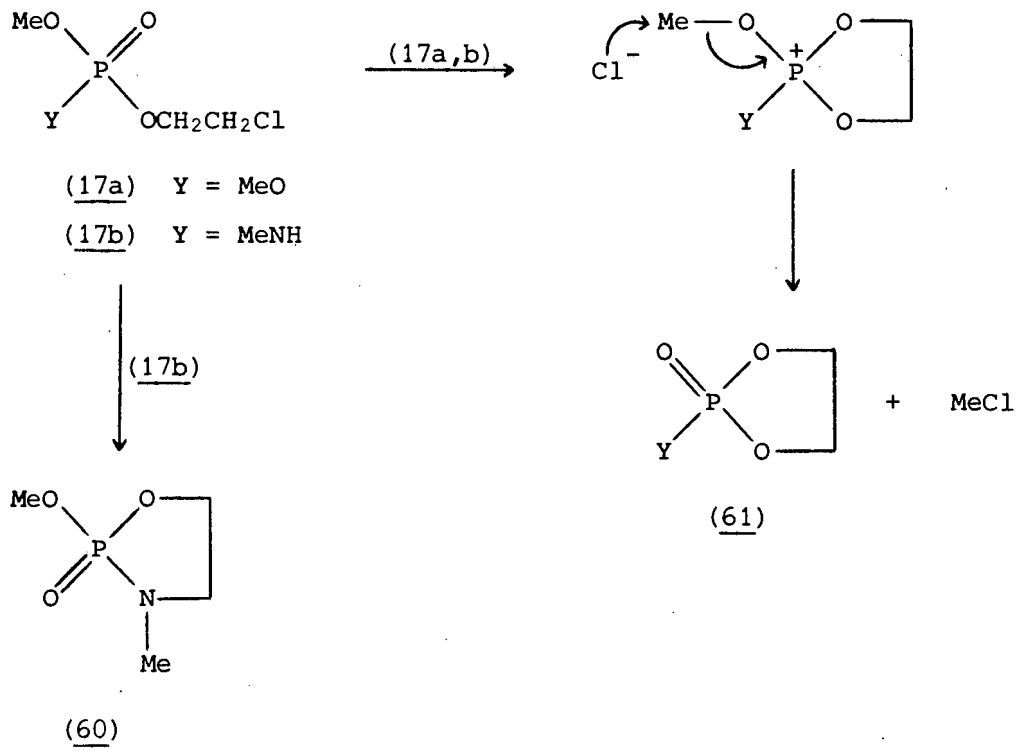
(17a), a high-boiling liquid, was purified by distillation and (17b), a viscous oil, was purified by column chromatography. Both compounds could be stored for several months without deterioration.



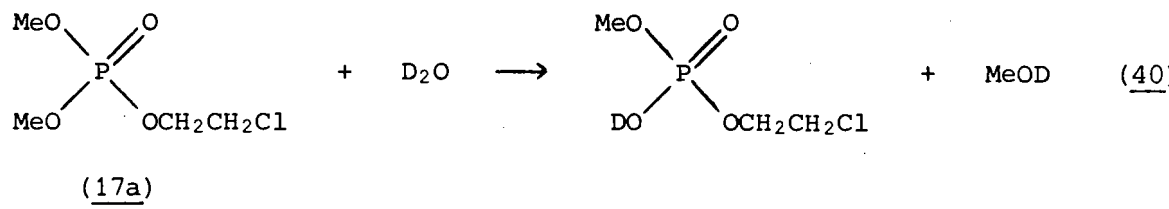
Scheme 5

The intramolecular reactions of (17) were investigated. These substrates cannot undergo 1,3-substitution. Dimethyl-(β-chloroethyl)phosphate (17a) can react only *via* the phosphoryl oxygen atom yielding the ester (61) (see Scheme 6). N-methyl methyl-(β-chloroethyl)phosphoramidate (17b) is capable of reaction *via* the phosphoryl oxygen atom as well as the amidate nitrogen atom as shown in Scheme 6. Both reactions involve 1,5 attack and formation of a five-membered cyclic product and intermediate.

The triester (17a) was treated with a solution containing an equimolar amount of silver oxide in deuterium oxide. Nucleophilic displacement of the chloride ion by the phosphoryl oxygen atom did not take place as no cyclic product was observed after 24 hours at 60° C. The only minor product obtained was deuteriomethanol (*ca.* 4%), formed by simple hydrolysis of (17a) as shown in Eq. 40.



Scheme 6

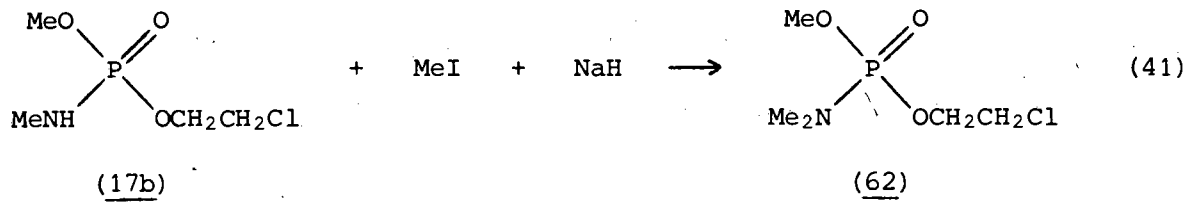


Since a similar proportion of deuteriomethanol is obtained when (17a) is treated with deuterium oxide alone and through similar treatment of trimethyl phosphate, it is clear that formation of deuteriomethanol is not dependent on the reactivity of the β-carbon atom in (17a).

Intramolecular nucleophilic displacement of the chloride ion by the amidate nitrogen in (17b) would yield the cyclic amidoester (60) which can be distinguished easily from (17b) by ^{1}H n.m.r. spectroscopy.[24] An analogous cyclisation product (5) was formed when cyclophosphamide (4) was treated with excess NaH (Chapter 1, Scheme 1, pathway a).[3] When (17b) was heated under

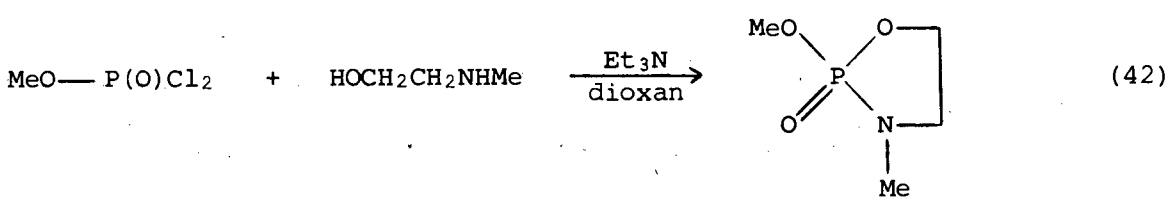
reflux for 5 hours in tetrahydrofuran containing a two-fold excess of sodium hydride, more than 90% of the unreacted substrate was recovered. Thus the cyclisation of (4) to yield (5) as reported by Zon[3] was not achieved for (17b).

In the presence of an equimolar quantity of an alkylating reagent such as iodomethane, (17b) reacts smoothly to yield the tertiary phosphoramidate (62) (Eq. 41).



(17b) (62) (41)

(62), a pale yellow oil, was identified by its ^{1}H n.m.r. spectrum (see Chapter 7.3), which differs from the spectrum of (17b) only with respect to the intensity and multiplicity of the PNMe signal. For (17b) this signal (δ 2.63) is a doublet of doublets integrating for three hydrogen atoms while for (62) it is a doublet integrating for six hydrogen atoms. This reaction (Eq. 41) demonstrates that the amidate nitrogen atom in (17b) is capable of acting as a nucleophile in alkylation reactions. The failure to form the 5-membered cyclic compound (60) by intramolecular displacement of the chloride ion may be analogous to that described for (15). It is interesting to note, however, that (60) can be prepared easily from methyl phosphorodichloridate and 2-(methylamino)ethanol (Eq. 42).[24]

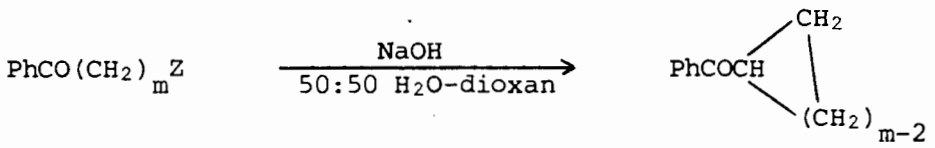


(42)

(60)

Since the ring closure step in Eq. 42 must also involve 1,5 nucleophilic substitution it seems that attack by an amine (or alcohol) nucleophile on the $\rangle P(O)Cl$ centre is much easier than the reaction involving attack by the nucleophilic group $\rangle P(O)N\langle$ at the β-carbon atom in (15) or (17b).

In conclusion, no evidence was found for intramolecular displacement of the halide ion from the β-haloethyl group by either of the amide nitrogen atoms or the phosphoryl oxygen atom to produce five-membered cyclic substitution products (see Scheme 3). Under conditions of electrophilic or basic catalysis intramolecular 1,3-substitution yielding the ethylenimine derivative represents the main (if not exclusive) course of reaction. These results parallel the findings of Stirling[49] *et. al.* who reported that the rate of formation of cyclopropanes by cyclisation of ω-halogenoalkyl ketones in base (Eq. 43) was up to 23 000 times faster than that of cyclopentanes, notwithstanding the very much larger ring strain in the smaller ring.



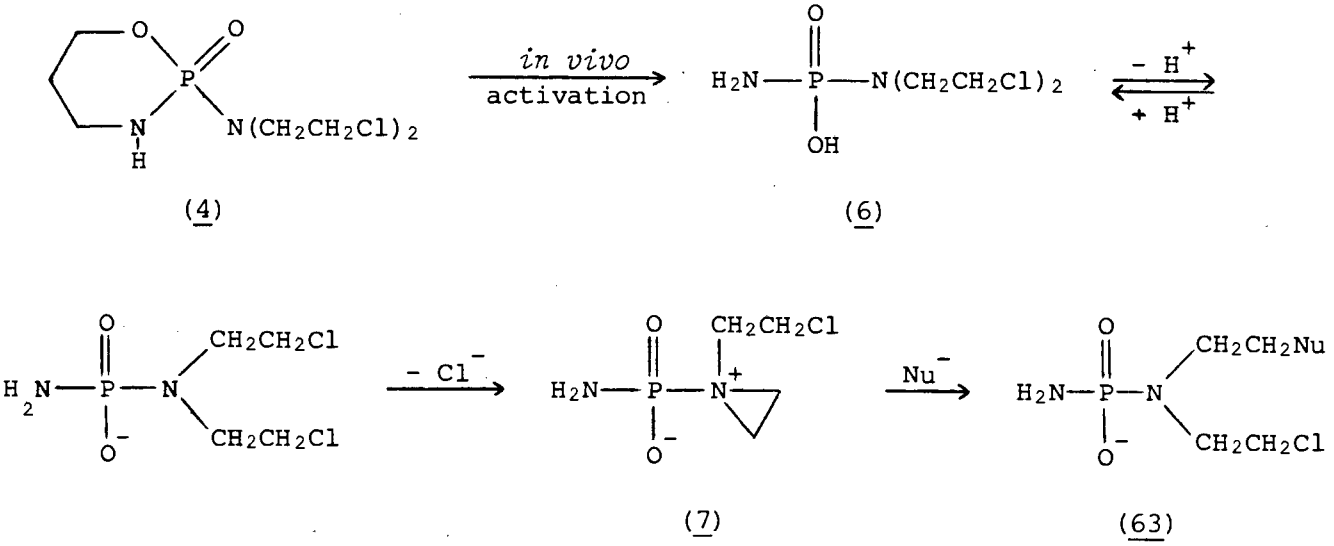
(43)

Z = Cl, Br; m = 3,5

The difference between the rate of formation of three- *vs.* five-membered rings in the phosphoramidates (15) and (16) could be even greater than that reported by Stirling as no five-membered cyclic products were observed in the intramolecular nucleophilic displacement of the chloride ion in (15) and (16).

The products isolated after *in vitro* hydrolysis of cyclophosphamide (4) at 100°C in water support a mechanism in which intramolecular alkylation resulting in the bicyclic product (5) is the initial step in the hydrolytic process (Scheme 1, pathway a). This pathway appears, however, to be an unlikely model

for the metabolic transformations of (4) *in vivo*.[5] The cytotoxic activity of (4) is due to *in vivo* activation of the substrate,[4] releasing the nitrogen mustard (6) which is a potent alkylating agent at physiological pH.[7] The greater alkylating activity of the phosphorodiamidic acid (6) relative to its ester derivative (4) is attributed to the enhanced rate of formation of the ethyleniminium derivative (7) by intramolecular cyclisation of the conjugate base of (6). (7) is a reactive alkylating agent due to the presence of the strained ethyleniminium ring and reacts with biological nucleophiles to give a monosubstituted intermediate (63) which can in turn form a second ethyleniminium ion and subsequently afford a disubstituted bisalkylated product.[7] The sequence of reactions described is shown in Scheme 7.

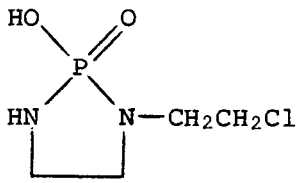


(4) (6) (7) (63)

Scheme 7

Thus although cyclophosphamide (4) is capable of intramolecular reaction yielding a five-membered cyclic product (5) when hydrolysed or treated with NaH,[3] the biological reactivity of this compound is due to the formation of the ethyleniminium derivative (7) from the nitrogen mustard (6).[7] It must be

noted that compound (6) has two amidate nitrogens. Thus intramolecular displacement of the chloride ion could in principle give rise to a five-membered cyclic derivative as (64) as well as the three-membered cyclic derivative (7).



(64)

The absence of product (64) is in agreement with the observation of the much greater preference for 1,3 *vs.* 1,5 cyclisation observed in the phosphoramidates (15) and (16).

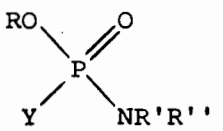
CHAPTER FOUR

ELECTRON IMPACT-INDUCED FRAGMENTATION PATHWAYS OF PHOSPHORAMIDATES

4.1 INTRODUCTION

In Chapter 3 it was shown that the nitrogen atom of phosphoramidates containing an N-(β-chloroethyl) group has strong nucleophilic reactivity. Although several reaction pathways are available in these phosphoramidates (see Schemes 2 and 3) there is a clear preference for the formation of three-membered rings *via* nucleophilic displacement of the chloride ion by the amidate nitrogen atom. These compounds also exhibit nucleophilic reactivity towards external alkylating agents and again the nitrogen atom acts as a nucleophile (Chapter 3.2.2).

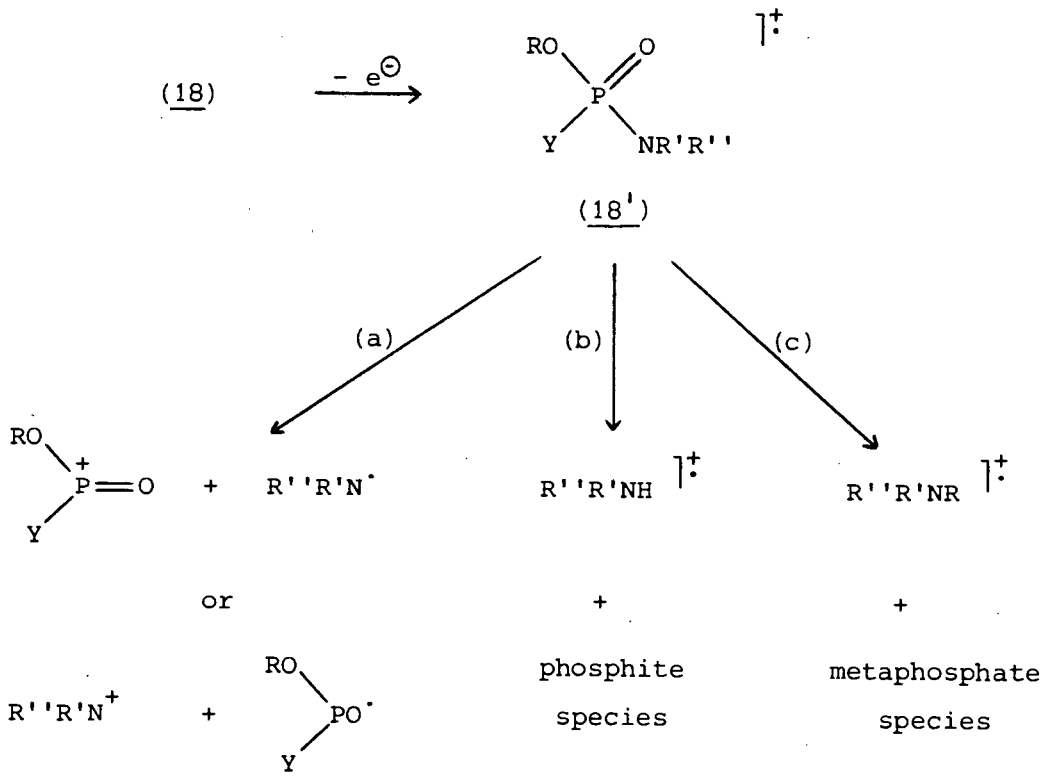
As discussed in Chapter 2, phosphoramidates are greatly activated towards solvolytic cleavage by an initial protonation step. This activation results from the introduction of a positive charge in the substrate and more specifically from the exact location of the charge on the nitrogen atom. Positively-charged phosphoramidates can also be formed when these compounds are bombarded by a stream of electrons at 70 eV. The positive charge of the molecular ion formed under these conditions is located in the $\rangle P(O)N\langle$ moiety[17] thus conferring an element of uniformity on the fragmentation pathways which occur. The unimolecular reactions of phosphoramidates after activation by Ag^+/OH^- or NaH were also studied and the results have been discussed in Chapter 3. We were therefore interested in the unimolecular reactions which occur under conditions of electron impact where these compounds are activated by removal of an electron. It was decided to examine the mass spectra of a series of phosphoramidates of the general structure (18) as there is little data available in the literature on the fragmentation pathways of this class of compound.



(18)

A large number of compounds was studied in order to determine the general fragmentation pathways for these compounds. A study of the electron impact-induced fragmentations of the phosphoramidates will contribute to the knowledge of the gas-phase behaviour of these compounds, *i.e.*, under conditions where medium effects and intermolecular reactions are absent.

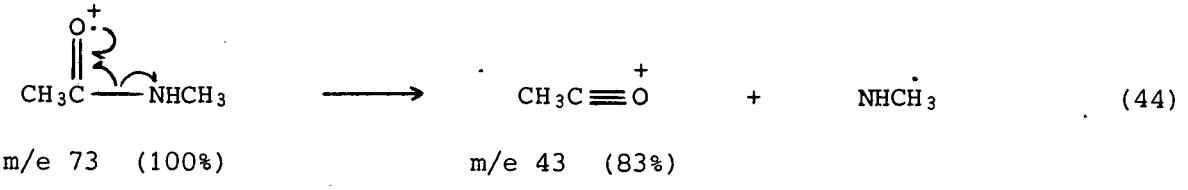
As the ionisation of (18) probably involves one of the electrons of the phosphoramidate function,[17] the P-N bond in the molecular ion (18') formed would be expected to be much more labile than in the parent substrate. The unimolecular cleavage of the P-N bond can then, in principle, follow any of the three pathways (a - c), shown in Scheme 8.



Scheme 8

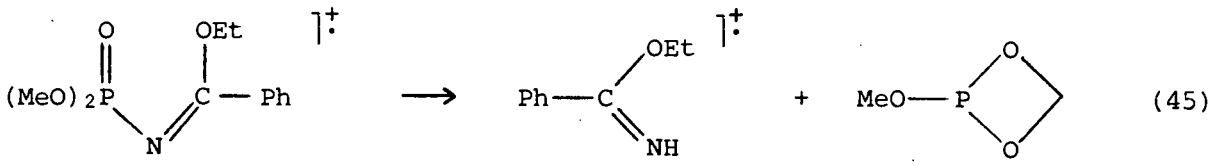
Simple cleavage of the P-N bond, pathway (a), has been observed before[16, 18] and in this respect substrates (18) fragment in a similar manner to carboxylic amides.[19]

In carboxylic amides having an alkyl group on the carbonyl function and no γ carbon atom in the alkyl group on the nitrogen atom, the molecular ion or the fragment resulting in cleavage of the bond α to the carbonyl group is often the most intense ion in the spectrum (Eq. 44).[19]



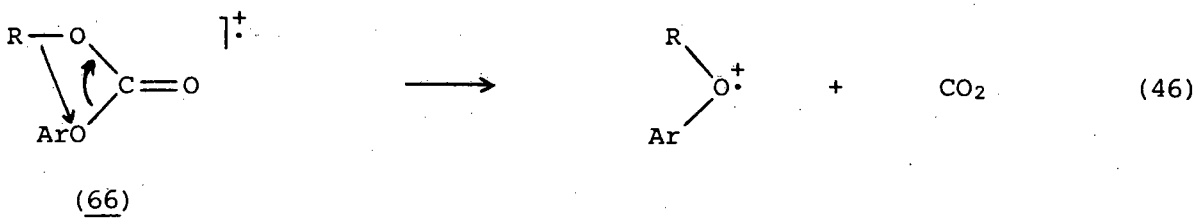
m/e 73 (100%) m/e 43 (83%) (44)

Pathway (b), which involves hydrogen migration to give an amine radical ion, requires release of a neutral phosphite molecule. This fragmentation has been proposed in the interpretation of the mass spectrum of O-ethyl-N-(dimethylphosphoryl)benzimidate (65) recorded in this laboratory[20] and it was thus of interest to establish the scope of this rearrangement (Eq. 45).

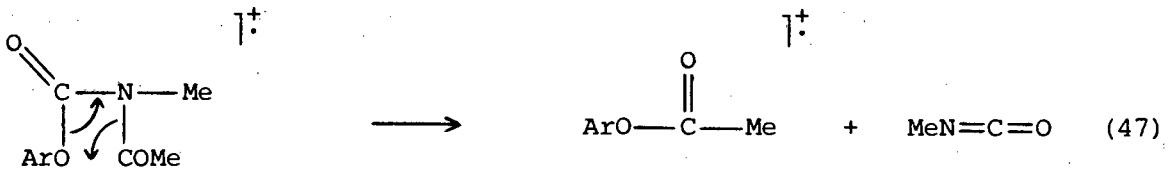


(65) (45)

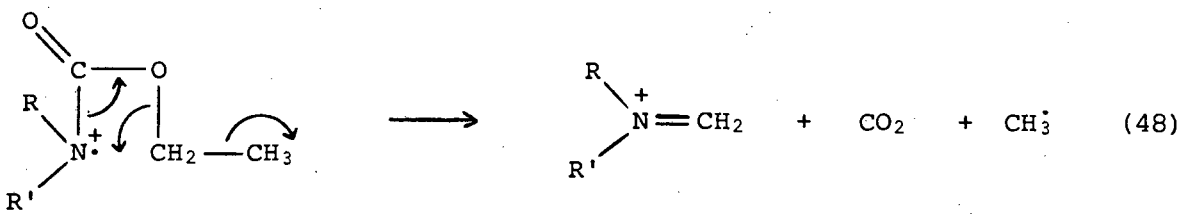
P-N bond cleavage accompanied by migration of an ester R group from the oxygen to the nitrogen atom, pathway (c), can be related to the well-established electron impact-induced fragmentations of carbonates (66)[21] and carbamates (67)[22a] and (68)[22b,c] involving O → O or O → N migration and expulsion of carbon dioxide or methyl isocyanate (Eq. 46 - 48).



(66) (46)

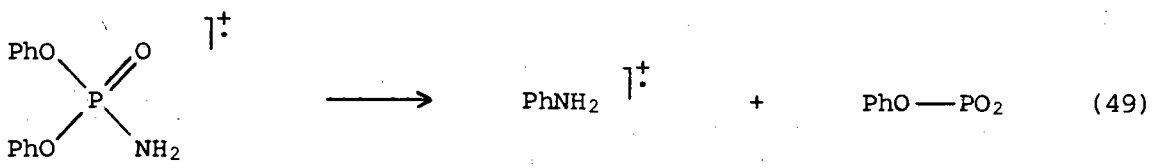


(67) (47)



(68) (48)

The migration of a phenyl group from oxygen to nitrogen accompanied by P-N bond cleavage has been reported but not discussed in the spectrum of diphenylphosphoramidate (69) (Eq. 49).[18]



(69) (49)

An investigation of the fragmentation behaviour of phosphoramidates and phosphoric esters containing the β-chloroethyl group, compounds (15) — (17), was carried out and compared with that reported for cyclophosphamide, (4).[23] Fragmentation pathways of a general nature for compounds (15) — (18), (21) and (22) are also discussed.

4.2 RESULTS AND DISCUSSION

The mass spectra of the following compounds were recorded and are discussed in Chapter 4.

$X(MeNH)P(O)NHCH_2CH_2Cl$ (15)

a: X = MeO

b: X = PhO

$X_2P(O)NHCH_2CH_2Cl$ (16)

a: X = MeO

b: X = PhO

c: X = Et

d: X = Ph

$Y(MeO)P(O)OCH_2CH_2Cl$ (17)

a: Y = MeO

b: Y = MeNH

$(RO)_2P(O)NR'R''$ (18A)

R = Me; R' = H

a: R'' = Me

b: R'' = Et

c: R'' = ^{i}Pr

d: R'' = ^{t}Bu

e: R'' = Ph

f: R'' = 2-MeC_6H_4

g: R'' = 3-MeC_6H_4

h: R'' = 4-MeC_6H_4

(18A) R = Me; R' = H

i: R'' = 2-EtC_6H_4

j: R'' = 4-EtC_6H_4

k: R'' = 4-$nBuC_6H_4$

l: R'' = 3,4-$Me_2C_6H_3$

m: R'' = 2,6-$Me_2C_6H_3$

n: R'' = 4-$MeOC_6H_4$

o: R'' = 3-$NO_2C_6H_4$

p: R'' = 4-$PhOC_6H_4$

q: R'' = 4-PhC_6H_4

r: R'' = 4-FC_6H_4

R = CD_3; R' = H

s: R'' = Ph

t: R'' = 4-MeC_6H_4

R = Et; R' = H

u: R'' = Me

v: R'' = Ph

R = Me; R' = D

w: R'' = Ph

$(PhO)_2P(O)NR'R''$ (18B)

R' = H

a: R'' = Me

b: R'' = Et

c: R'' = ^{i}Pr

d: R'' = ^{t}Bu

e: R'' = CH_2Ph

f: R'' = CH(Me)Ph

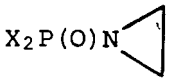
g: R'' = $CH_2C_6H_4$-4-Me

h: R'' = Ph

R' = Me

i: R'' = Me

$(MeO)_2P(O)NMe_2$ (21)



(22)

a: X = MeO

b: X = Et

c: X = Ph

Selected fragmentation data are listed in Tables 4 - 9. General fragmentation schemes for (15), (16), (17), (18A) and (21), (18B) and (22) are shown in Figures 3 - 8 and the mass spectra of (15b), (17b), (18Ae), (18Ba) and (22a) are shown in Figures 9 - 13.

The last page of Chapter 4, containing the formulae of all the compounds discussed, can be folded out for the convenience of the reader.

Table 4 Fragmentation data for (15); fragment ion (% relative abundance)

Compound	$[M]^{+\cdot}$	$[M-CH_2Cl^{\cdot}]^{+}$	$[(RO)(MeNH)P{=}O]^{+}$	$[M-CH_2{=}CHCl]^{+\cdot}$	$[RNHMe]^{+\cdot}$	$[RNMe]^{+}$	$[MeNH]^{+}$	$[M-Cl^{\cdot}]^{+}$
a[1]	186(4)	137(100)	108(94)	124(5)	-	-	(28)	151(4)
b[2]	248(34)	199(94)	170(32)	186(10)	107(65)	106(19)	(95)	213(9)

1 $[MeNHCH_2CH_2Cl]^{+\cdot}$ m/e 93(2) 2 m/e 155(12)

Table 5 Fragmentation data for (16); fragment ion (% relative abundance)

Compound	$[M]^{+\cdot}$	$[M-CH_2Cl^{\cdot}]^{+}$	$[X_2P{=}O]^{+}$	$[M-CH_2{=}CHCl]^{+\cdot}$	$[M-Cl^{\cdot}]^{+}$
a[1]	187(6)	138(100)	109(64)	125(4)	152(4)
b[2]	311(35)	262(100)	-	-	276(7)
c[3]	183(4)	134(100)	105(47)	-	148(14)
d	-	230(53)	201(100)	217(3)	244(8)

1 $[(MeO)(H)P{=}O]^{+}$ m/e 79(19); $[MeNHCH_2CH_2Cl]^{+\cdot}$ m/e 93(5)

2 $[(PhO)P(O)NCH_2]^{+}$ m/e 168(9); $[PhNHCH_2CH_2Cl]^{+\cdot}$ m/e 155(4)

3 $[(Et)(H)P{=}O]^{+}$ m/e 77(18)

Table 6 Fragmentation data for (17); fragment ion (% relative abundance)

Compound	$[M-CH_2Cl^{\cdot}]^{+}$	$[(MeO)(Y)P{=}O]^{+}$	$[(MeO)(H)P{=}O]^{+}$	$[M-CH{=}CHCl^{\cdot}]^{+}$	$[(HO)(Y)P{=}O]^{+}$	$[M-Cl^{\cdot}]^{+}$
a	139(36)	109(100)	79(12)	127(57)	95(14)	153(83)
b[1]	138(10)	108(100)	79(13)	126(17)	94(18)	152(69)

1 $[MeNH]^{+}$ m/e 30(90)

Table 7 Fragmentation data for (18A) and (21); fragment ion (% relative abundance)

Compound	$[M]^{+\cdot}$	$[(RO)_2P{=}O]^+$	$[(RO)(H)P{=}O]^+$	$[M\text{-}MeOH]^{+\cdot}$	$[R''R'NH]^{+\cdot}$	$[R''R'N]^+$	$[R''R'NR]^{+\cdot}$	$[R''R'NR\text{-}H^{\cdot}]^+$	$[M\text{-}X^{\cdot}]^+$
a	139(65)	109(90)	79(60)	107(4)	31(52)	30(100)	-	-	-
b	153(6)	109(60)	79(14)	-	45(2)	44(56)	-	-	138(100)[1]
c	167(3)	109(25)	79(14)	-	-	58(16)	-	-	152(100)[1]
d	-	109(12)	79(8)	-	-	72(2)	-	-	166(100)[1]
e	201(100)	109(21)	79(15)	169(39)	93(48)	92(26)	107(10)	106(52)	-
f	215(87)	109(10)	79(16)	183(11)	107(18)	106(100)	121(4)	120(21)	-
g	215(100)	109(12)	79(25)	183(45)	107(55)	106(50)	121(7)	120(36)	-
h	215(100)	109(10)	79(21)	183(60)	107(21)	106(45)	121(5)	120(25)	-
i	229(48)	109(9)	79(10)	-	121(18)	120(100)	135(4)	134(11)	214(23)[1]
j	229(43)	109(6)	79(7)	-	121(9)	120(9)	-	134(3)	214(100)[1]
k	257(32)	109(9)	79(7)	-	-	-	-	-	214(100)[2]
l	229(100)	109(11)	79(8)	197(50)	121(11)	120(21)	135(2)	134(10)	-
m	229(67)	109(5)	79(6)	197(10)	121(12)	120(100)	-	134(4)	-
n	231(100)	109(51)	79(12)	199(20)	123(2)	122(23)	-	-	216(73)[1]
o	246(77)	109(100)	79(23)	214(3)	138(6)	137(1)	-	-	200(16)[3]
p	293(100)	109(18)	79(7)	261(20)	185(5)	184(14)	199(3)	-	216(9)[4]
q	277(100)	109(6)	79(4)	245(28)	169(8)	168(13)	-	182(4)	-
r	219(100)	109(65)	79(14)	187(41)	125(5)	124(23)	111(6)	110(28)	-
s	207(100)	115(23)	82(10)	172(36)	94(41)	93/92(32)[5]	110(9)	109/108(27)[5]	-
t	221(100)	115(13)	82(5)	186(65)	108(17)	107/106(19)[5]	124(4)	123/122(10)[5]	-
u	167(10)	-	-	-	31(72)	30(100)	59(6)	-	-
v	229(67)	137(6)	-	-	93(56)	92(36)	121(3)	120(11)	-
w	202(100)	109(24)	79(12)	169(28)	94(44)	93(31)[6]	108(9)	107(43)[6]	-
						92(10)[7]		106(18)[7]	
(21)	153(34)	109(48)	79(30)	-	45(36)	44(100)	-	-	138(20)[1]

1 X = CH_3 2 X = C_3H_7

3 X = NO_2 4 X = Ph

5 loss of $H^{\cdot}$ or $D^{\cdot}$; peaks are of similar intensity

6 loss of $H^{\cdot}$ 7 loss of $D^{\cdot}$

Table 8 Fragmentation data for (18B); fragment ion (% relative abundance)

Compound	$[M]^{+\cdot}$	$[(PhO)(R''R'N)P{=}O]^{+}$	$[R''R'NH]^{+\cdot}$	$[R''R'N]^{+}$	$[R''R'NPh]^{+\cdot}$	$[R''R'NPh\text{-}H^{\cdot}]^{+}$	$[PhOH]^{+\cdot}$	$[Ph]^{+}$
a	263(50)	170(70)	-	30(28)	107(21)	106(18)	(44)	(100)
b	277(45)	184(23)	45(2)	44(72)	121(9)	120(6)	(38)	(100)
c[1]	291(14)	-	-	-	-	-	(23)	(71)
d[1]	305(3)	-	-	-	-	-	(14)	(28)
e	339(57)	245(8)	107(21)	106(100)	183(7)	182(43)	(77)	(46)
f[1]	353(28)	260(6)	121(8)	120(86)	-	-	(29)	(62)
g	353(28)	260(4)	121(10)	120(100)	197(3)	196(16)	(26)	(20)
h[2]	325(100)	232(13)	93(8)	92(30)	-	168(25)	(30)	(60)
i	277(32)	184(23)	45(3)	44(100)	121(4)	120(11)	(27)	(46)

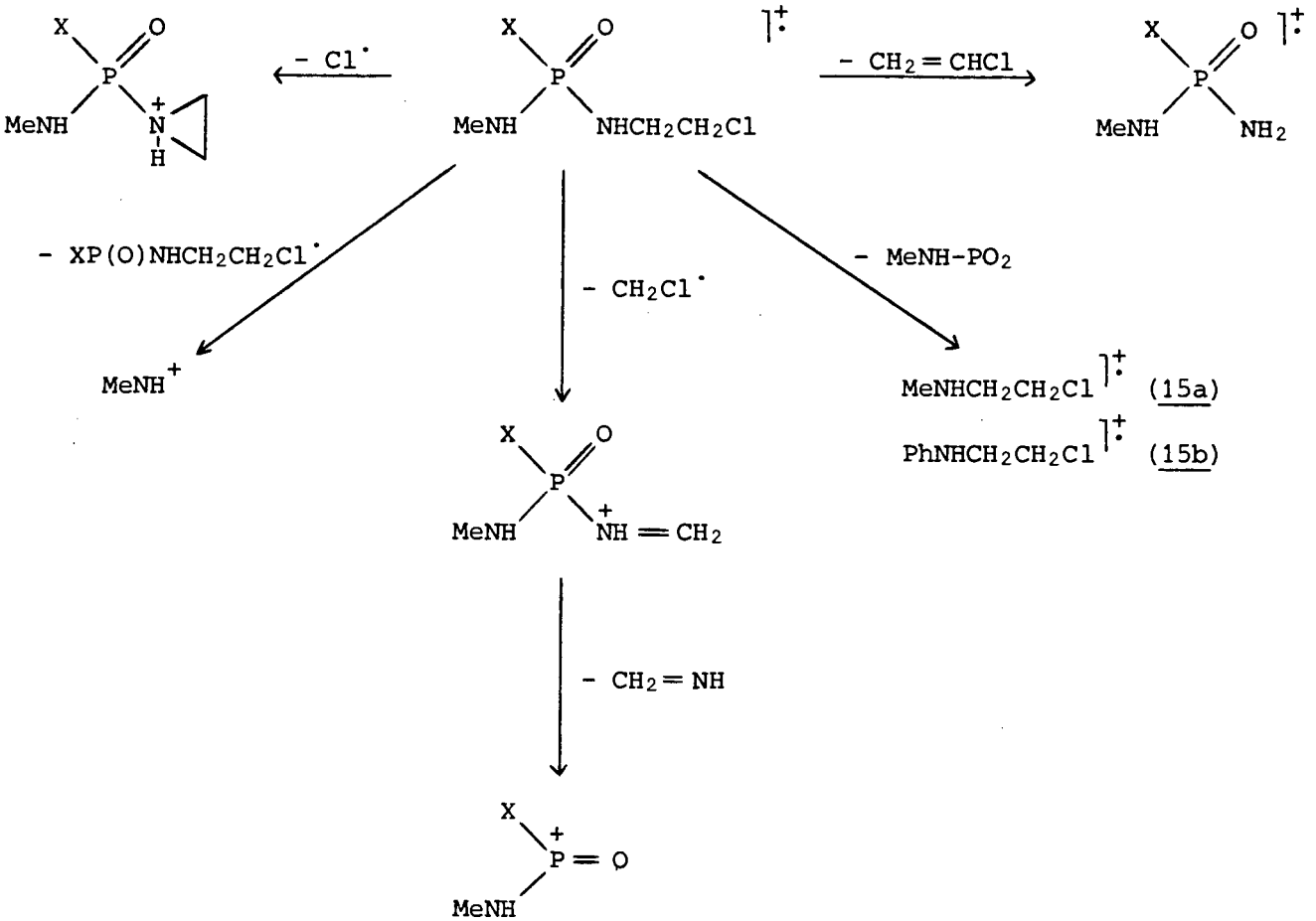
1 base peak is $[M\text{-}CH_3^{\cdot}]^{+}$ 2 m/e 170(9); m/e 169(13)

Table 9 Fragmentation data for (22); fragment ion (% relative abundance)

Compound	$[M]^{+\cdot}$	$[X_2P{=}O]^{+}$	$[M\text{-}CH_2{=}CH_2]^{+\cdot}$	$[M\text{-}C_2H_3^{\cdot}]^{+}$	$[C_2H_4N]^{+}$
a[1]	151(2)	109(26)	123(8)	124(9)	(100)
b	147(100)	105(82)	119(39)	120(3)	(46)
c	243(53	201(100)	215(31)	216(18)	(44)

1 $[(MeO)(H)P{=}O]^{+}$ m/e 79(19); $[C_2H_5N]^{+\cdot}$ m/e 43(43); $[MeN\triangleleft]^{+\cdot}$ m/e 57(4)

Figure 3 General fragmentation scheme for X(MeNH)P(O)NHCH$_2$CH$_2$Cl (15)



In particular, when X = PhO (15b)

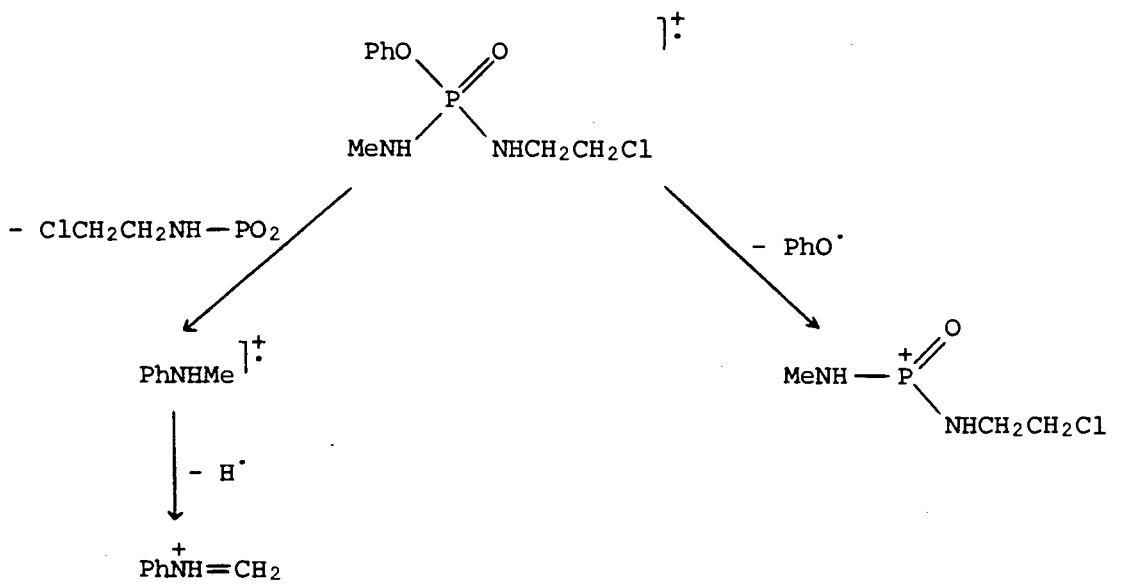


Figure 4 General fragmentation scheme for $X_2P(O)NHCH_2CH_2Cl$ (16)

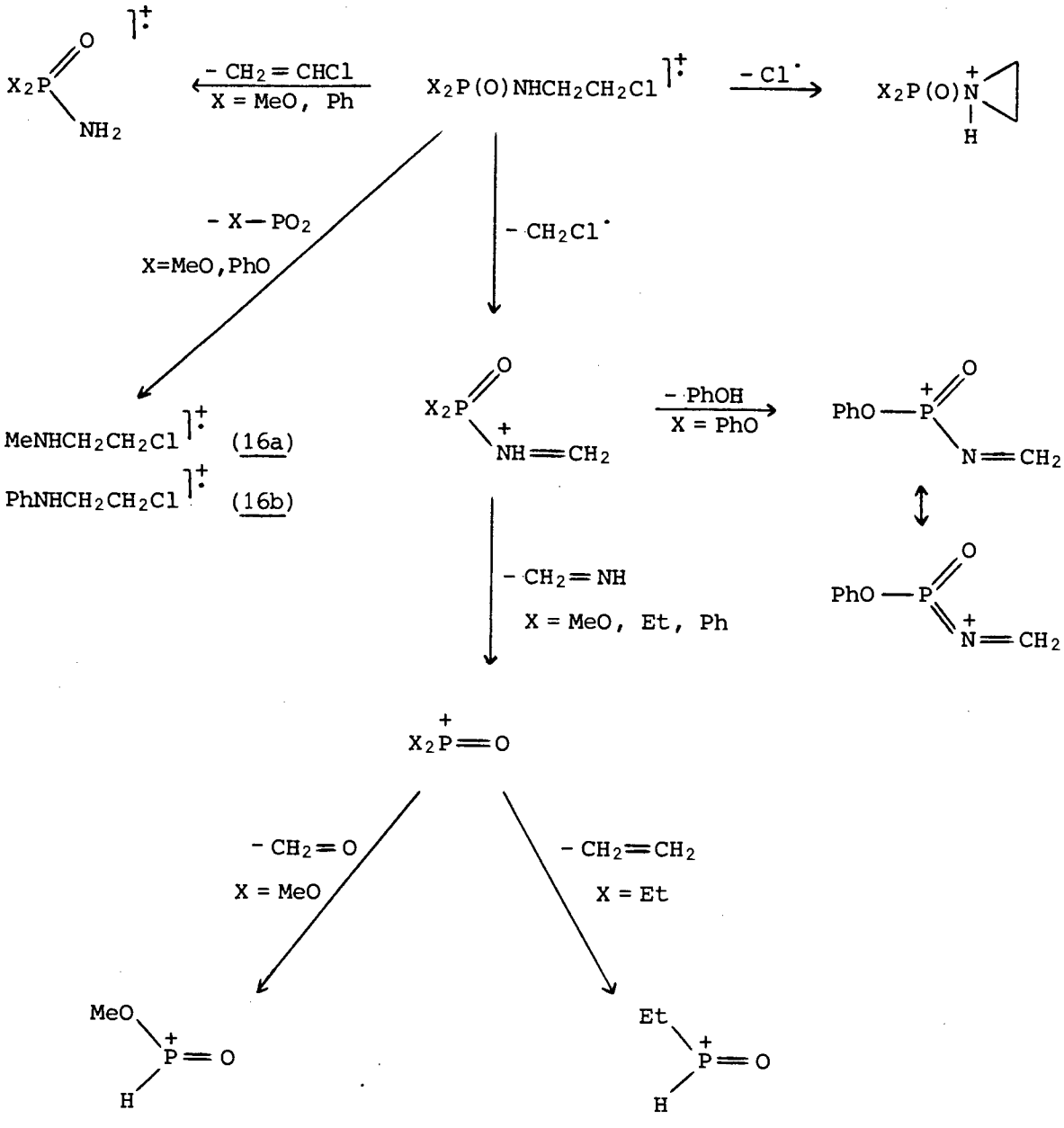
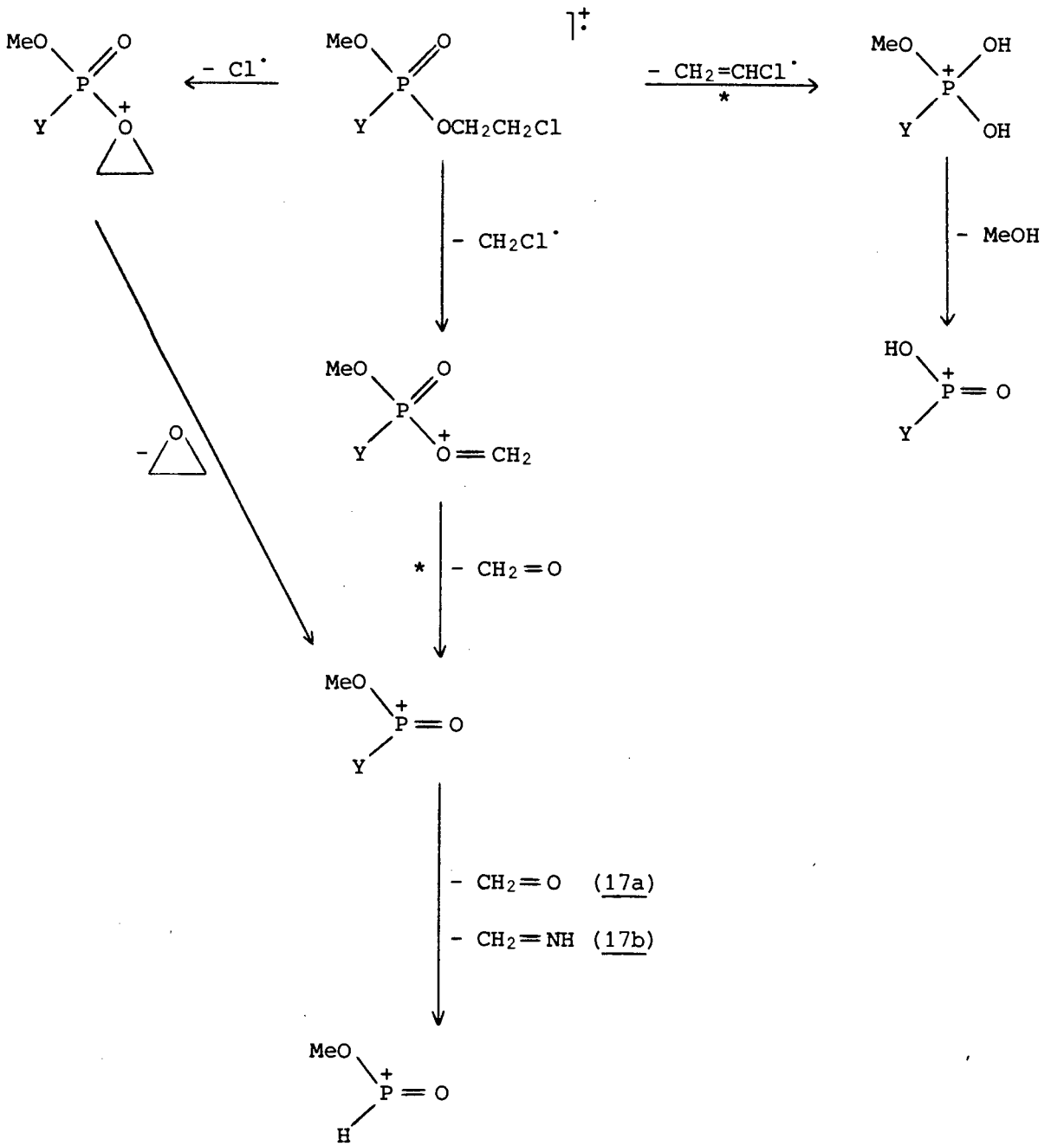


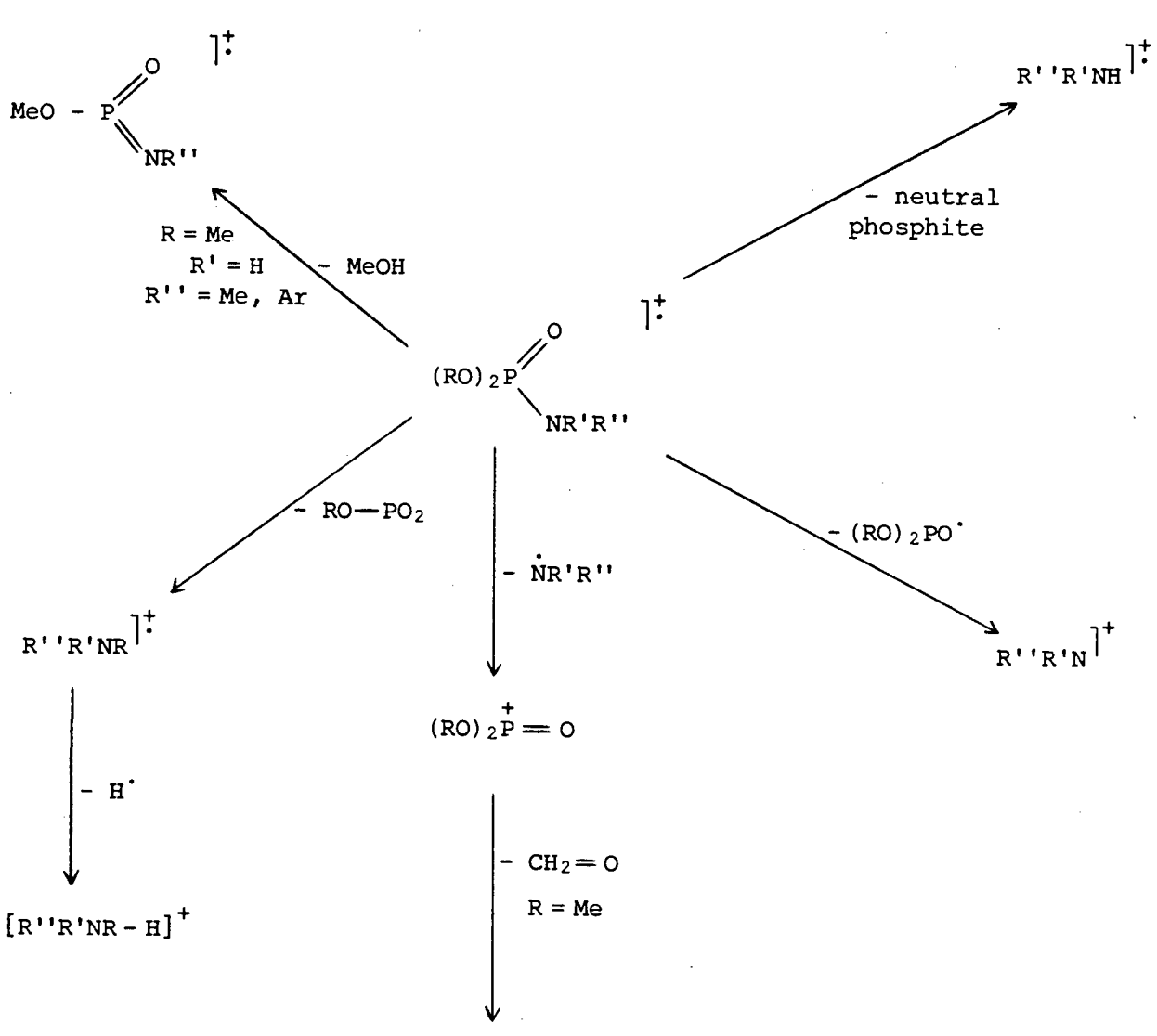
Figure 5 General fragmentation scheme for Y(MeO)P(O)OCH_2CH_2Cl (17)



In particular, when Y = MeNH (17b); $[MeNH]^+$ m/e 30 is formed.

*For (17a) the metastable peaks calculated for these fragmentations have very similar values (85.47; 85.79). Thus unambiguous assignment is not possible. Therefore the maximum number of pathways which can be supported by the observed metastable peak, m/e 85.4 - 85.7, are presented.

Figure 6 General fragmentation scheme for $(RO)_2P(O)NR'R''$ (18A) and $(MeO)_2P(O)NMe_2$ (21)



In particular, when R = Et, R' = H (18u,v)[16]

$$(EtO)_2P(O)NHR''\,]^{+\cdot} \xrightarrow{-\,CH_2=CH_2} (EtO)(HO)P(O)NHR''\,]^{+\cdot}$$

Figure 7 General fragmentation scheme for $(PhO)_2P(O)NR'R''$ (18B)

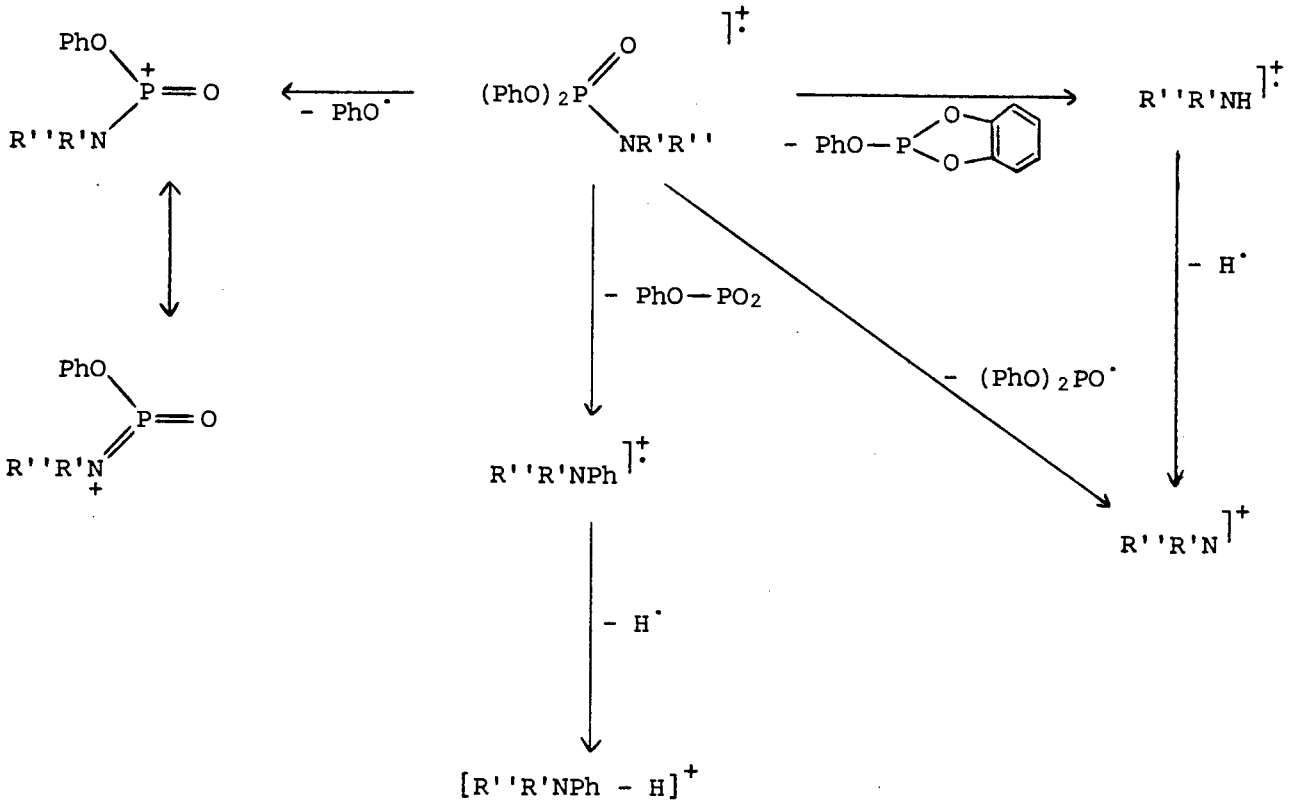
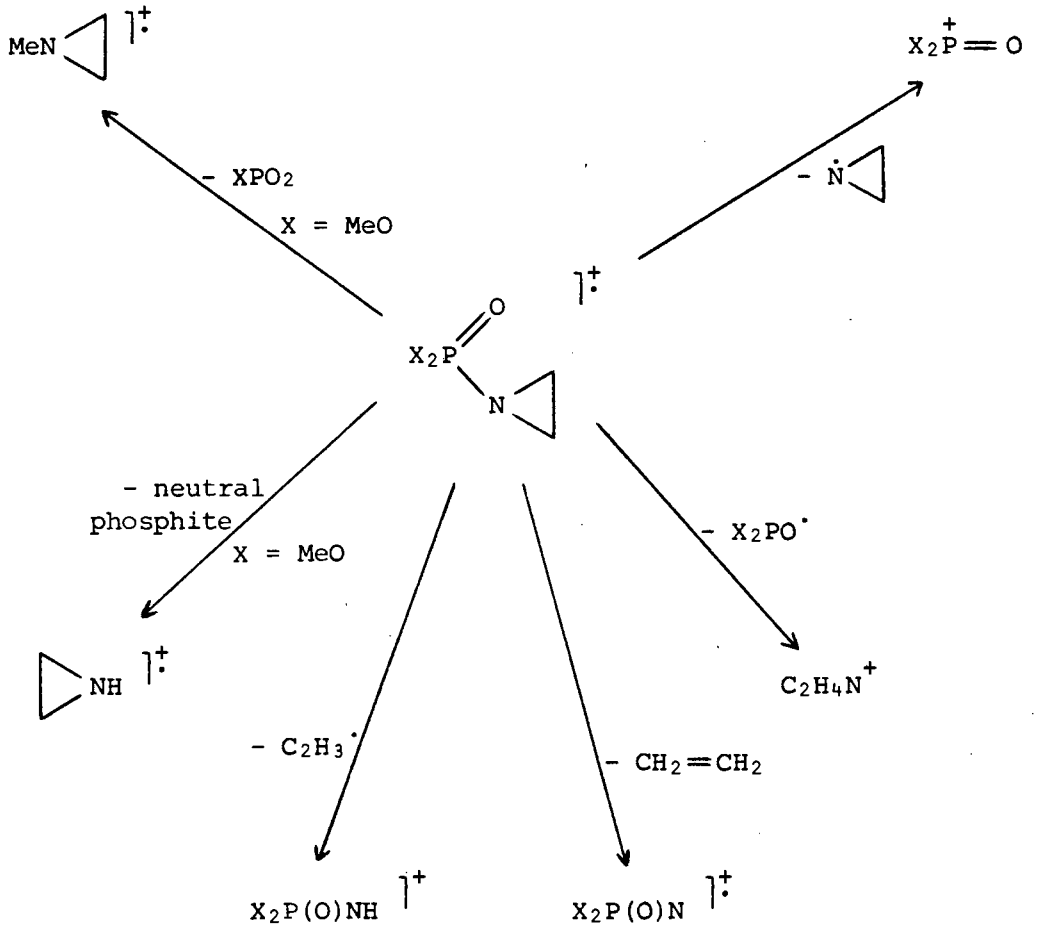


Figure 8 General fragmentation scheme for $X_2P(O)N$ (22)



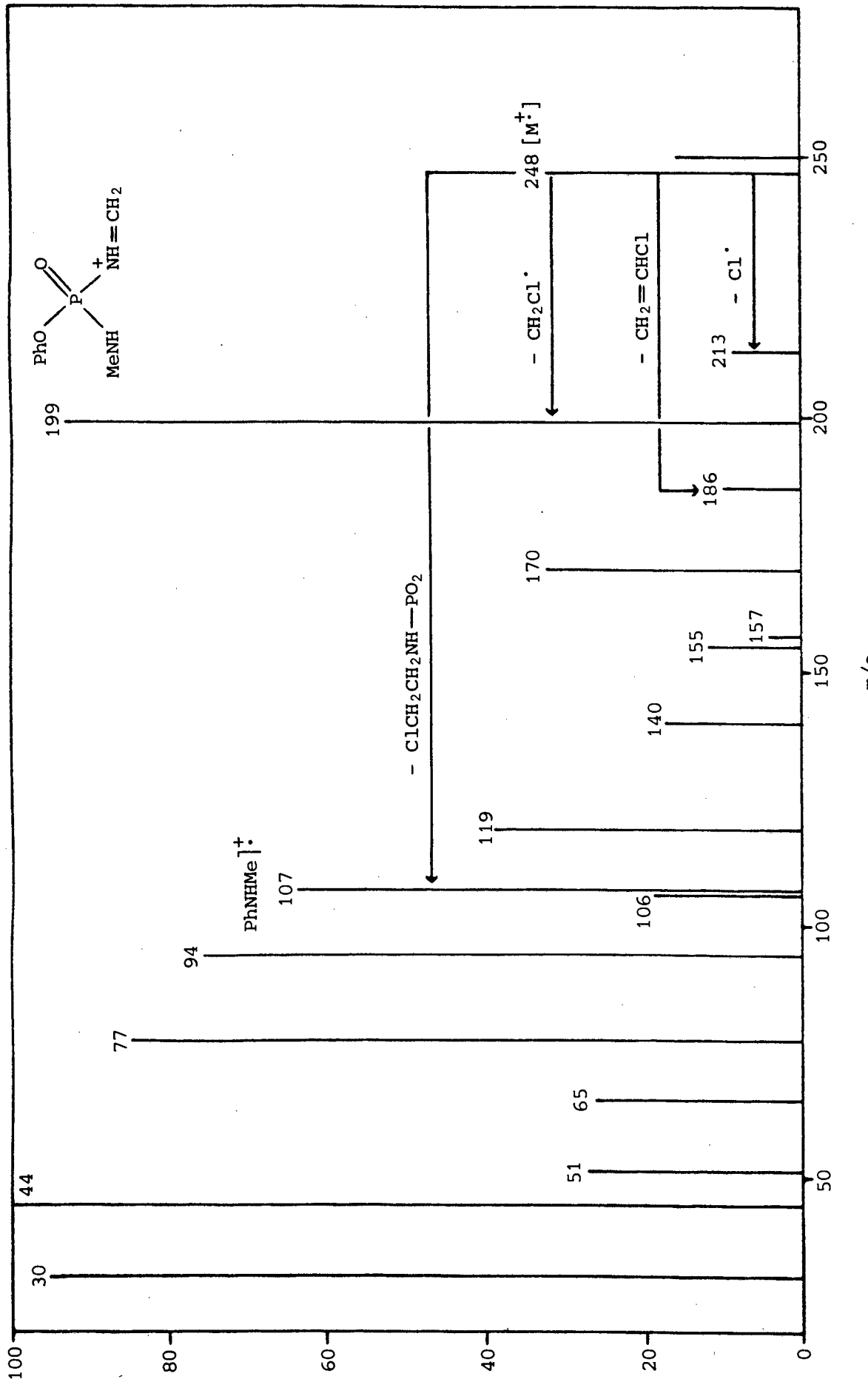


Figure 9 Mass spectrum of (PhO)(MeNH)P(O)NHCH$_2$CH$_2$Cl (15b)

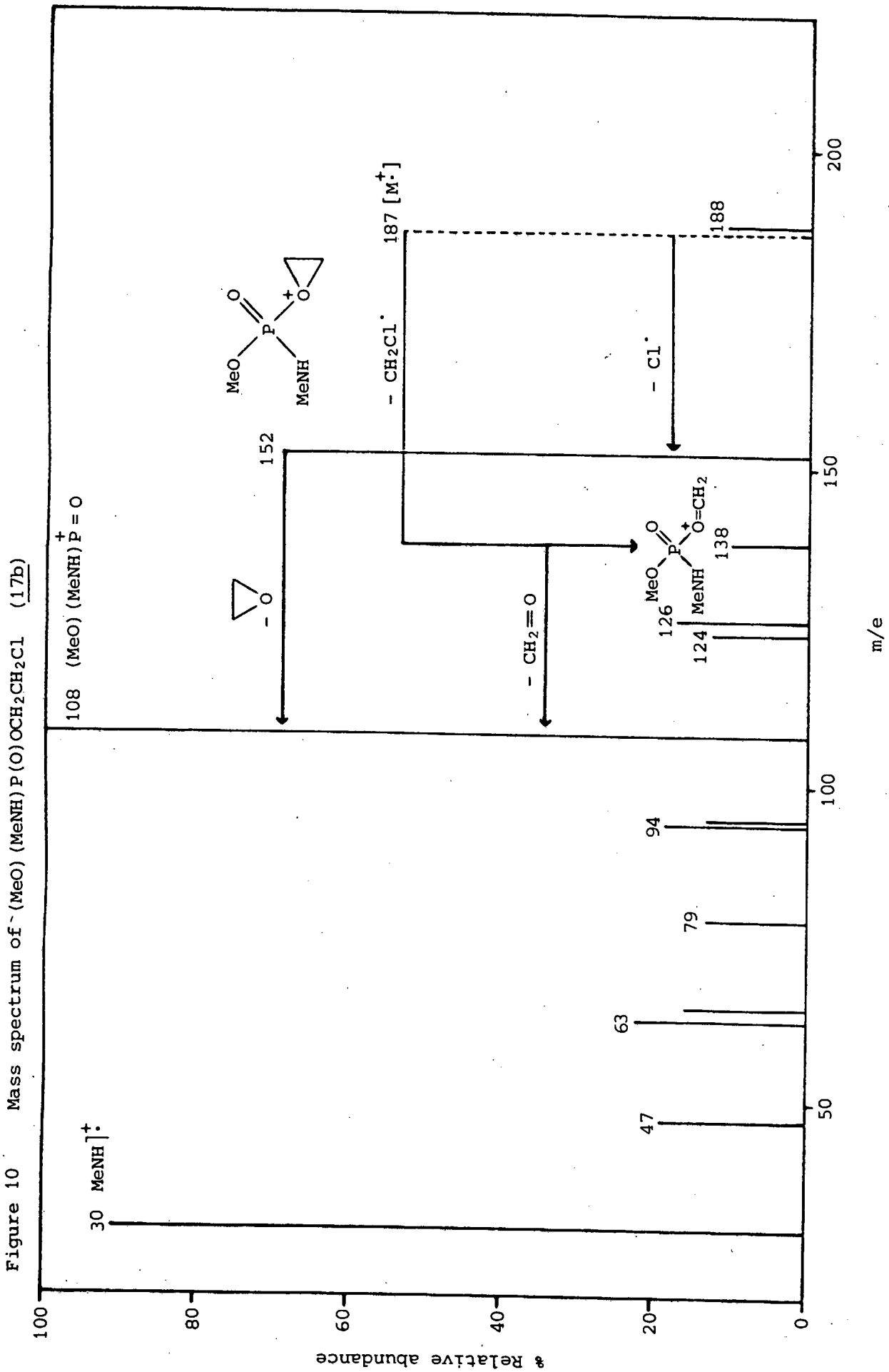


Figure 10 Mass spectrum of (MeO) (MeNH) P(O)OCH_2CH_2Cl (17b)

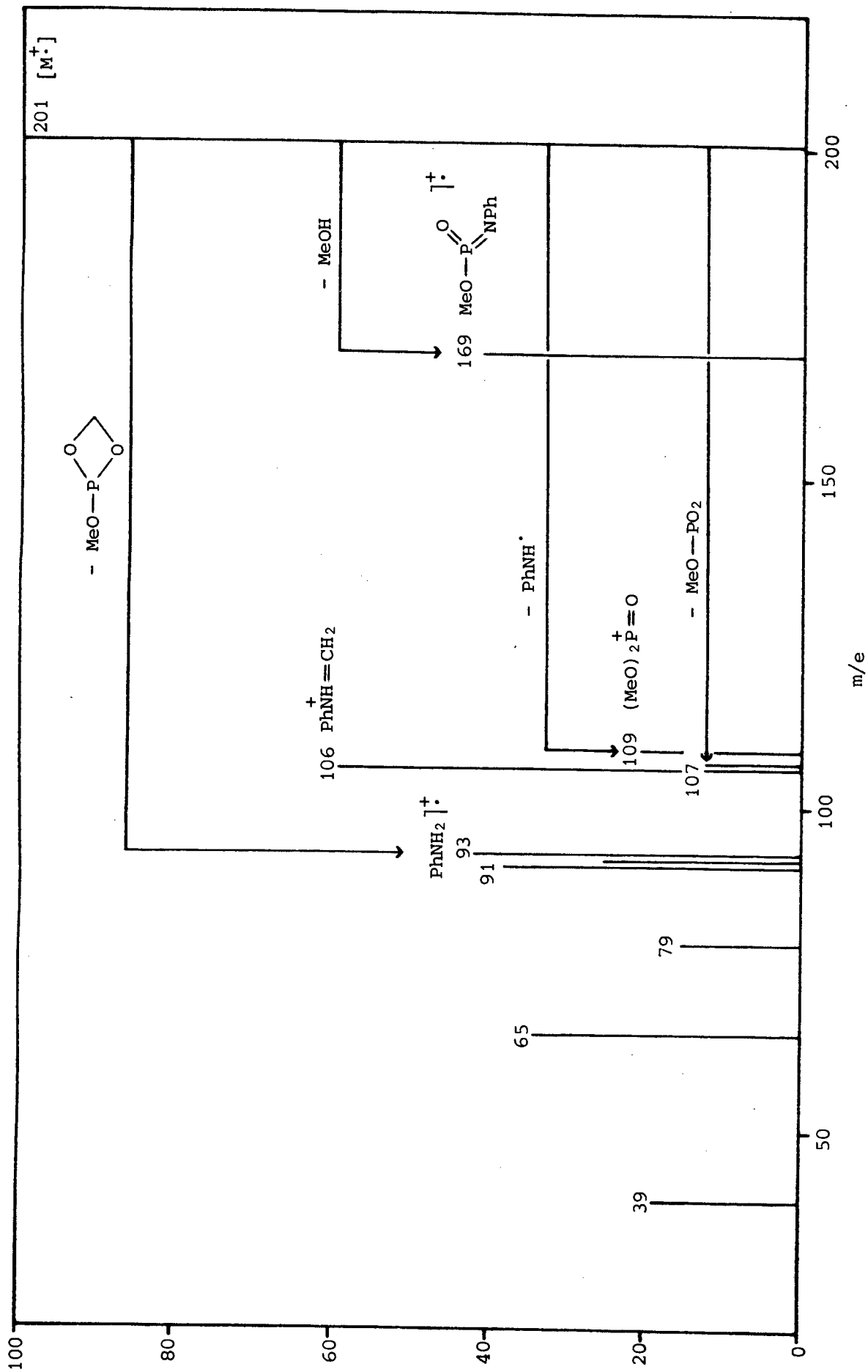


Figure 11 Mass spectrum of $(MeO)_2P(O)NHPh$ (18Ae)

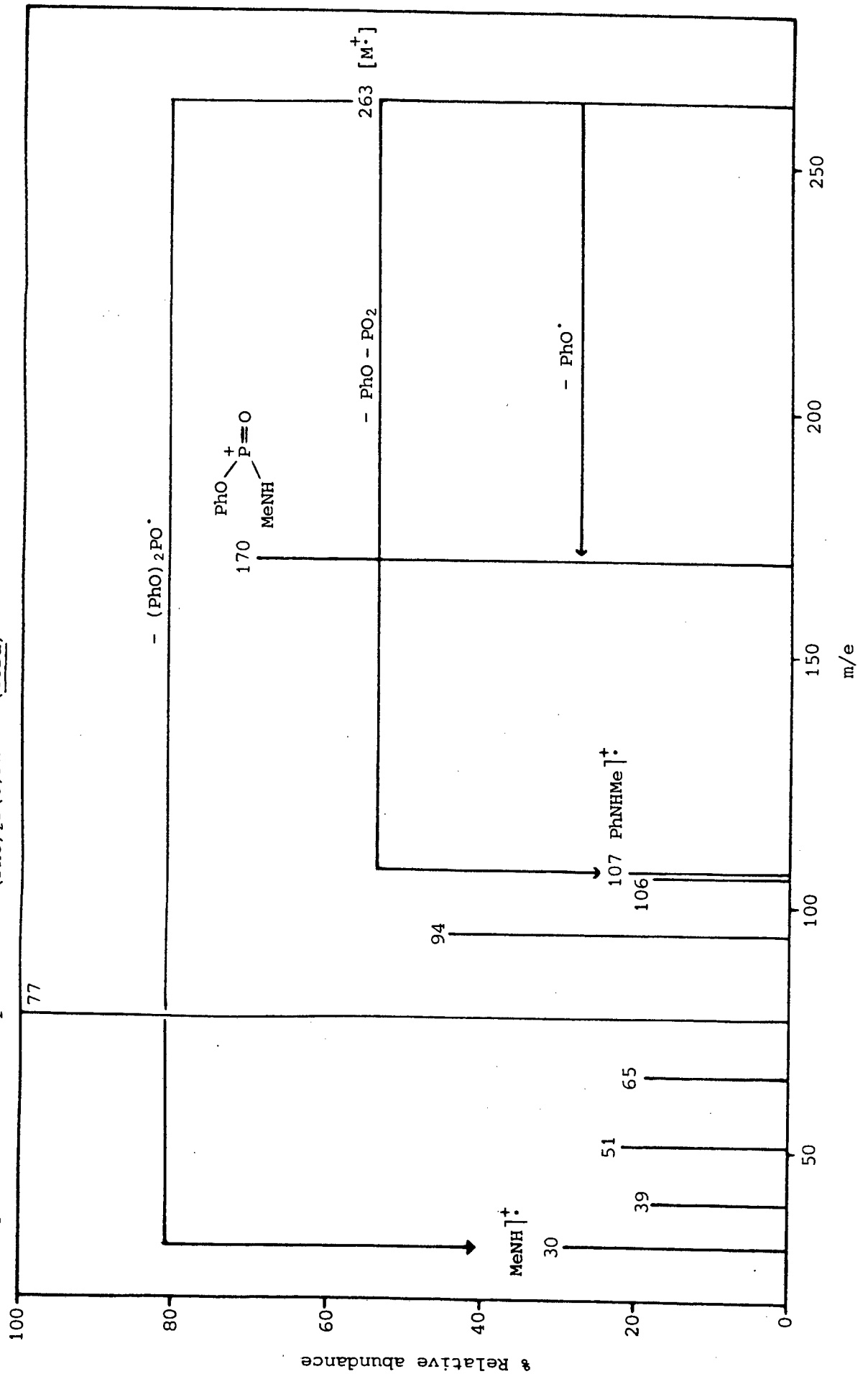


Figure 12 Mass spectrum of $(PhO)_2P(O)NHMe$ (18Ba)

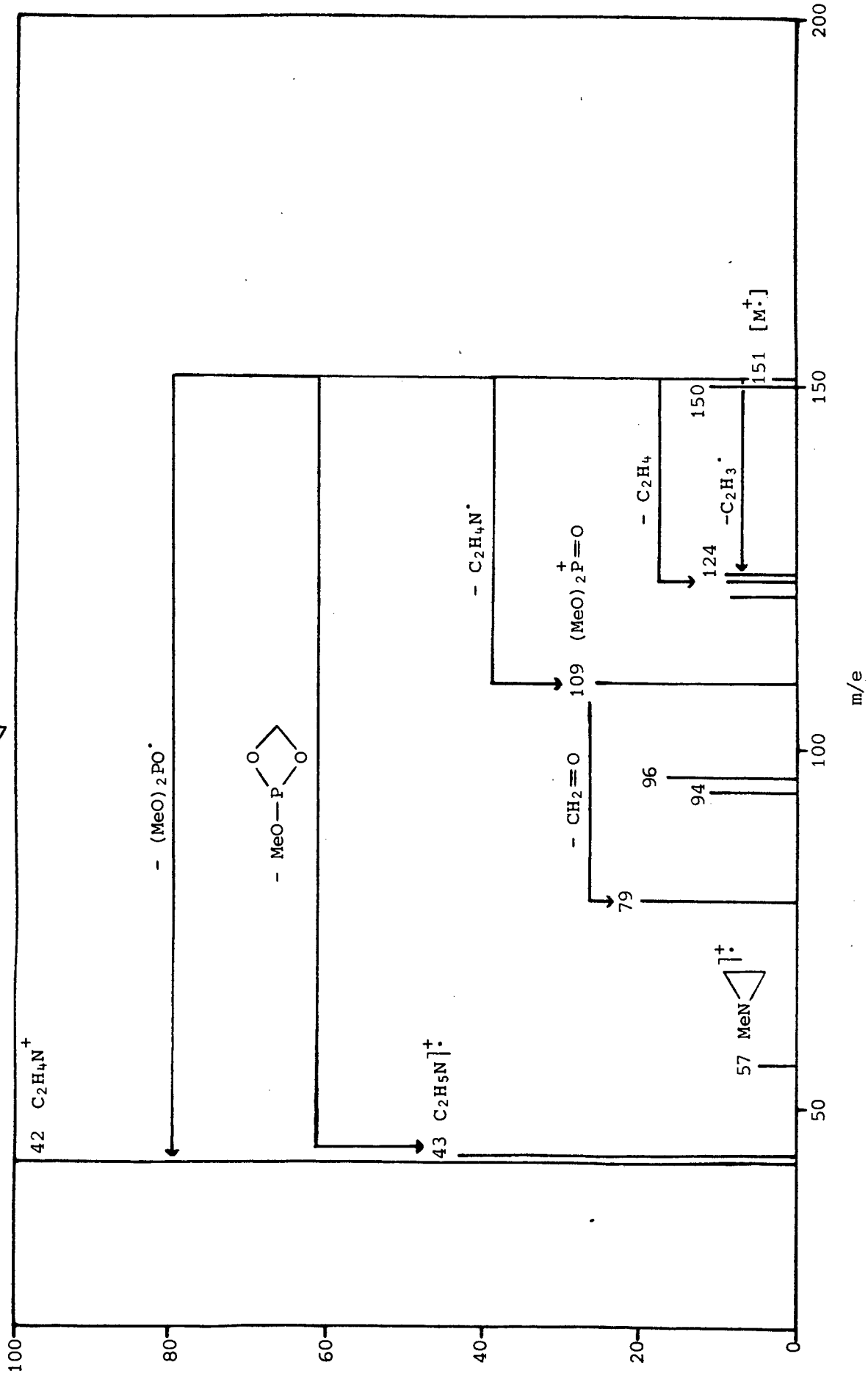


Figure 13 Mass spectrum of $(MeO)_2P(O)N$ (22a)

The electron-impact induced fragmentations of the phosphoramidates studied often gave rise to complex spectra. As attention was to be focussed on general trends within the different groups of compounds, the secondary fragmentations arising from substituents on the nitrogen or phosphorus atoms, *e.g.*, (18A), (18B) (R'' = alkyl or aryl) and (16c), (22b) (X = Et) are not described in this chapter.

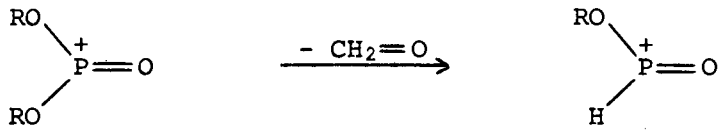
Molecular ions derived from all the compounds studied were relatively stable since they were observed for all compounds except (16d), (17a,b) and (18Ad) and varied in intensity from 2 to 100%.

4.2.1 SIMPLE P-N BOND CLEAVAGE

The simplest mode of P-N cleavage of the molecular ion is homolytic fission, Scheme 8 pathway (a), yielding a phosphorylium ion (70) and an amino radical (Eq. 50).

$$(RO)_2P(O)NR'R'' \,]^{+\cdot} \longrightarrow \underset{(70)}{(RO)_2\overset{+}{P}{=}O} + R''R'N^{\cdot} \qquad (50)$$

In agreement with previous reports,[16,50] formation of dialkylphosphorylium ions [(70), R = alkyl] was observed, in some cases as the base peak, for the substrates (18A) [except (18Au)], (21) and (22). This fragmentation was supported by metastable peaks for (18Ar), (18At), (22a) and (22c). When R = Me, the phosphorylium ion (70) eliminated methanal (see Eq. 51).[18,50] This pathway was supported by metastable peaks for (17a), (18Aa,d,e,j,k,n-t and w).

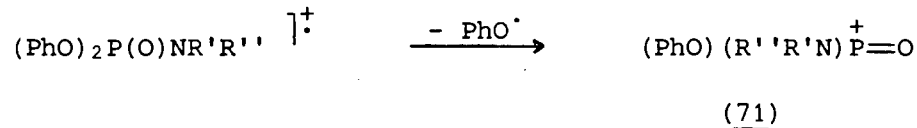


(51)

(70) R = Me

Homolytic bond fission of phosphoramidates and dialkylphosphinic acids and esters gives rise to phosphorylium[16, 18] or phosphinylium[51] ions under conditions of electron impact. There is, however, no evidence of the participation of phosphinylium ions in the reaction of phosphorus compounds in solution.[38] This contrasts with the behaviour of carboxylic amides, acids and esters where it is possible to generate the analogous acylium ions in solution[52] as well as in the gas phase by electron impact.[53]

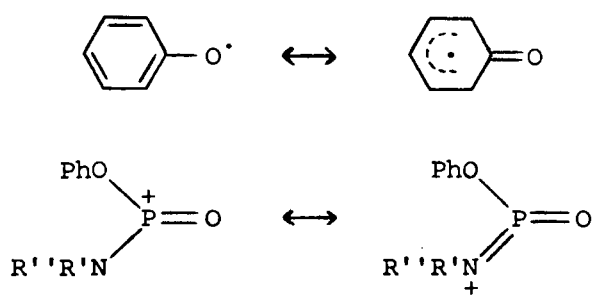
Fragmentation of molecular ions derived from substrates (18B) involved P-OAr, not P-N bond fission (Eq. 52); in this respect compounds (18B) behaved as aryl phosphates[54] rather than phosphoramidates. This pathway was supported by a metastable peak for (18Bh).



(52)

(71)

The selectivity of P-N *vs.* P-O cleavage is a function of the relative stabilities of the possible phosphorylium ions and radical species formed and reaction (52) is favoured probably by the resonance stabilisation of both the phenoxy radical and the nitrogen-containing phosphorylium ion (71) shown below.



(71)

In the mass spectrum of diphenyl phosphoramidate (69) the peak at m/e 170 (relative abundance 57%) was assigned to the diphenylether radical ion (72) formed by rearrangement of the molecular ion (Eq. 53).[18]

$$(PhO)_2P(O)NH_2\ ]^{+\cdot} \xrightarrow{-\ PO_2NH_2} PhOPh\ ]^{+\cdot} \qquad (53)$$

(69) (72)

The peak observed at m/e 170 in the spectrum of $(PhO)_2P(O)NHMe$ (18Ba) could be due to the phosphorylium ion (71) (R' = H, R'' = Me) formed by elimination of the phenoxy radical (see Eq. 52) or due to the diphenylether radical ion (72) formed by a rearrangement analogous to that shown in Eq. 53. It is known that measurement of the mass of an ion with sufficient accuracy provides unambiguous identification of its elemental composition, a technique known as "high resolution mass spectrometry."[55] The exact mass of the ion at m/e 170 was determined and the results are given in Table 10.

Table 10 Exact mass measurement of m/e 170 for (18Ba)

Exact mass:	calculated[1] for $C_7H_9NO_2P$	170.0369
	calculated for $C_{12}H_{10}O$	170.0732
	observed	170.0394

1 Nuclidic masses taken from Ref. 53, p. 275

Thus the peak at m/e 170 observed in the spectrum of (18Ba) is shown to be due to the phosphorylium ion $(R''R'N)(PhO)\overset{+}{P}{=}O$ (71) (R' = H, R'' = Me). A peak at m/e 156 was observed in the spectrum of (69) and this corresponds to (71) (R' = R'' = H).[18] The loss of phenoxy radical from the molecular ion yielding the phosphorylium ion (71) (Eq. 52) is thus a general fragmentation pathway for diphenylphosphoramidates.

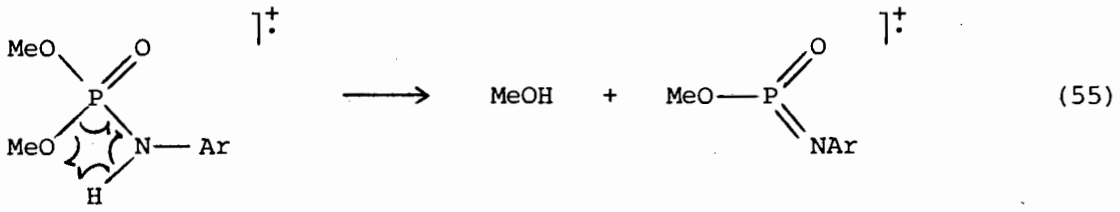
The formation of diphenylether radical ion (72) (m/e 170) was also observed in the spectrum of $(PhO)_2P(O)NHPh$ (18Bh).[56] In this respect compounds (69) and (18Bh) parallel the behaviour of triaryl phosphates which undergo rearrangement processes involving expulsion of a phosphorus atom and recombination of the aromatic nuclei with or without oxygen bridges.[54] The spectra of (69), (18Bh) and triphenylphosphate also show a peak at m/e 169 which has the composition $C_{12}H_9O$.[56] Substrates (18B) also parallel the behaviour of triaryl phosphates[54] by giving rise to the formation of the phenol radical ion and the phenyl cation.

The other possibility for pathway (a), (Scheme 8), is the liberation of an "amino cation" (73) and a phosphoryl radical (Eq. 54).

$$(RO)_2P(O)NR'R'' \,]^{+\cdot} \longrightarrow \underset{(73)}{R''R'\overset{+}{N}} + (RO)_2P\dot{O} \qquad (54)$$

This cleavage, which parallels the behaviour of N-substituted carboxamides,[19] was observed in compounds (15a,b), (17b), (18Aa,b,e-r,v,w) and (18Ba,b,e-h), *i.e.*, in substrates having a secondary amino group which yields, on fragmentation, an "amino cation", $R''NH^+$, where R'' = Me, Et, CH_2Ar, Ar but not for R'' = ^{i}Pr, ^{t}Bu. In common with N-methylcarboxamides[19] the mass spectra of phosphoramidates having an N-methyl group, (15a,b), (17b), (18Aa, 18Au) and (18Ba) contained a peak at m/e 30 due to the $MeNH^+$ ion. These "amino cations" can also be formed by a secondary fragmentation (discussed later) and since direct fission (Eq. 54) was confirmed by a corresponding metastable peak for only one substrate, (18Am), this type of fragmentation is probably not the most important mode of P-N bond cleavage. The spectra of compounds (22) exhibited a peak at m/e 42, which is assigned to the ion $C_2H_4N^+$, formed by P-N bond cleavage of the molecular ion.

A characteristic fragmentation which did not involve P-N bond fission was elimination of methanol from secondary N-aryl dimethylphosphoramidates, (18A), (R'' = aryl), probably *via* a four-membered transition state as shown in Eq. 55.



(55)

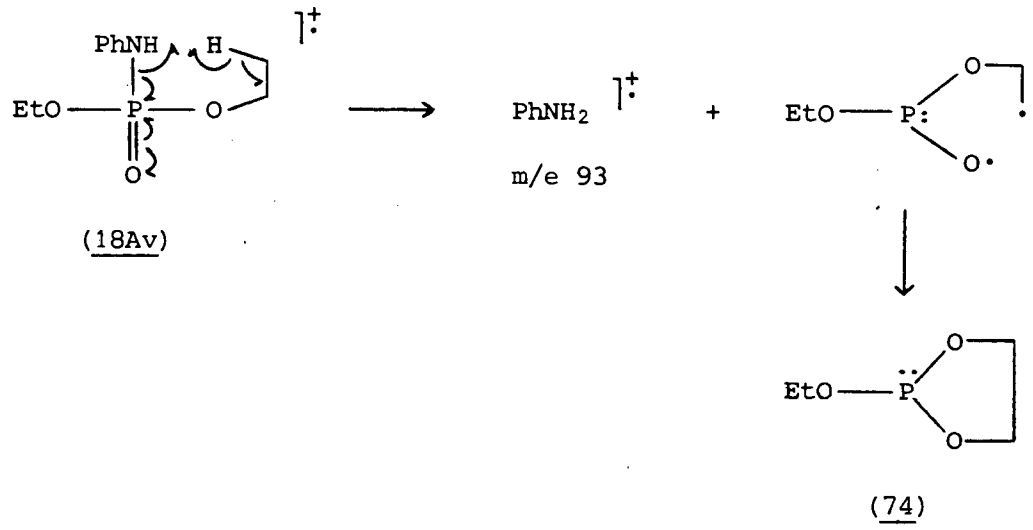
(18A)

Direct loss of methanol was supported by metastable peaks for most substrates except (18Ai-k), *i.e.*, for those where loss of an alkyl radical from the ring substituent is preferred.[57] The N-deuterated-N-phenyl derivative (18Aw) eliminated a molecule of MeOD giving the metaphosphate radical ion $(MeO)P(O)(NPh)]^{+\cdot}$ thus supporting the mechanism shown in Eq. 55.

4.2.2 P-N BOND CLEAVAGE ACCOMPANIED BY HYDROGEN MIGRATION

Another type of P-N bond cleavage in molecular ions derived from substrates (18) is represented by pathway (b) (Scheme 8) and is accompanied by hydrogen migration. The resultant formation of the amine radical ion involves expulsion of a molecule of neutral phosphite. Such a fragmentation was proposed in earlier work from this laboratory in the interpretation of the mass spectrum of O-ethyl-N-(dimethylphosphoryl)benzimidate (65).[20] In the present work, this fragmentation occurred in compounds (18Aa,b,e-w), (18Bb,e-h) and (22a) yielding the radical ion of the corresponding amine, $R''R'NH]^{+\cdot}$. This ion then fragmented according to the usual patterns characteristic of this class of compound. The peak (rel. intensity 57%) due to the aniline radical ion formed from the molecular ion of (18Av) involves the loss of ethyl ethylene

phosphite (74) possibly *via* the initially-formed diradical species. The proposed mechanism for this fragmentation is shown in Eq. 56.

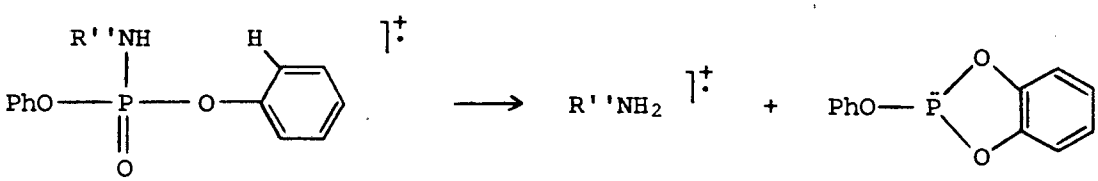


(18Av) (56)

(74)

The mass spectrum of (18Av) has been described; abundant fragments at m/e 93 and m/e 92 were assigned the structures $C_6H_7N]^{+\cdot}$ and $C_6H_6N^+$ respectively but no explanation for their formation was given.[56]

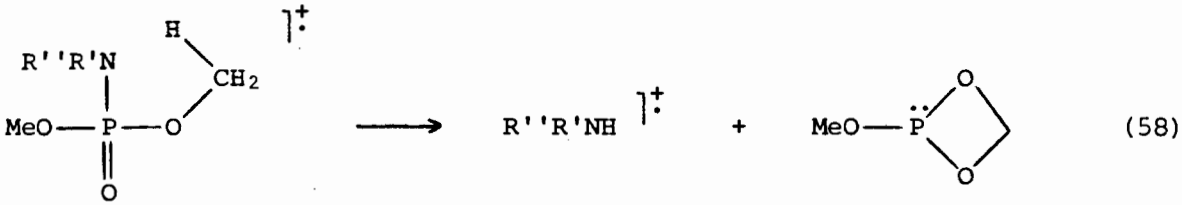
In the case of the phenyl esters (18B) the formation of an amine radical ion [supported by a metastable peak for (18Be)] indicates expulsion of a well-known[58] type of phosphite, *viz.* phenyl phenylene phosphite (75) (Eq. 57).



(18B) (57)

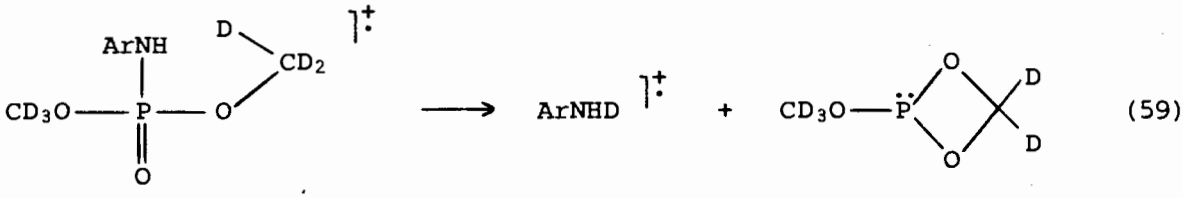
(75)

Release of the amine radical ion from methyl esters, observed previously in this laboratory[20] and supported by a metastable peak for (18Am) implies the analogous formation of methyl methylene phosphite (76) (Eq. 58).



(18A) (76) (58)

Although methylene phosphites of type (76) are not known, it is probably the synthetic difficulty rather than any intrinsic instability of such a system that make them inaccessible. The mass spectra of the two hexadeuterated substrates (18As) and (18At) were recorded. As expected the corresponding monodeuterated amine radical ions (m/e 94 and 108; rel. intensity 41 and 17% respectively) were observed (Eq. 59).

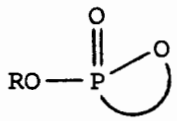


(59)

(18A) s: Ar = Ph m/e 94

t: Ar = 4-MeC_6H_4 m/e 108

It should be noted that the cyclic phosphite esters RO—P<O,O) postulated as the neutral products formed by P-N bond cleavage accompanied by hydrogen migration (see Eq. 56 - 59) are isomeric with the corresponding phosphonic acid esters (77).



(77)

In the case of products (74) and (76), however, the isomeric structure (77) would involve the formation of small, strained four- and three-membered rings, respectively. It is postulated therefore that the phosphite ester structures (74) - (76) are more likely representations of the neutral species formed in

the fragmentations shown in Eq. 56 - 59.

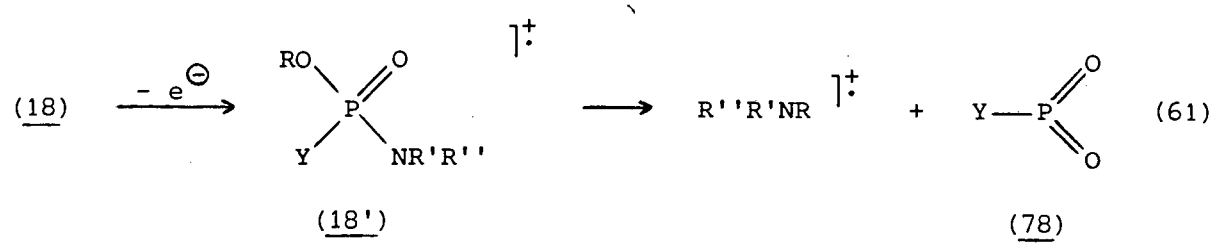
In all cases the amine radical ion $R''R'NH]^{+\cdot}$ is accompanied by an $(M-1)^+$ peak (often of greater intensity), formed by loss of a hydrogen atom during secondary fragmentation; this is typical for amines (Eq. 60).[59]

$$R''R'NH\,]^{+\cdot} \xrightarrow{-\,H^{\cdot}} R''R'N^{+} \qquad (60)$$

Thus the fragment $R''R'N^+$ observed in the mass spectra recorded in this work could originate either from simple cleavage of the P-N bond of the molecular ion (18) [Scheme 8, pathway (a)] or by the fragmentation of $R''R'NH]^{+\cdot}$ formed by P-N cleavage of (18) accompanied by hydrogen migration [Scheme 8, pathway (b)].

4.2.3 P-N BOND CLEAVAGE ACCOMPANIED BY OXYGEN TO NITROGEN MIGRATION

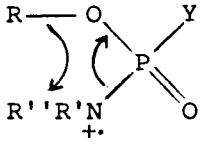
The most interesting mode of electron impact-induced fission of the P-N bonds in compounds (18) is that involving the migration of the ester R group from oxygen to nitrogen [Scheme 8, pathway (c)]. This fragmentation was found for both alkyl [(15a), (16a) and (18A)] and phenyl [(15b), (16b) and (18B)] amidoesters as well as for the N-phosphorylated ethylenimine (22a). It can be represented as shown in Eq. 61.



(61)

The expulsion of a metaphosphate species (78) in this migration parallels the release of carbon dioxide observed in the spectra of carbonates[21] and some

carbamates.[22] While the release of a thermodynamically stable molecule of CO_2 can provide the driving force for the migration observed for carbonates and carbamates, Eq. 61 illustrates the gas-phase formation of the very unstable metaphosphate structure (78).* Nevertheless, the fragmentation represented by Eq. 61 seems to be of a general nature and was observed for substrates (15a,b), (16a,b), (18Aa,e-i,l,p-w), (18Ba,b,e,g,h) and (22a) [confirmed by metastable peaks for (15b), (18Ae,s,t,w), (18Bb,e)]. The spectrum of *(PhO)(MeNH)P(O)*$NHCH_2CH_2Cl$ (15b) was also measured at 11 eV, *i.e.* just above the ionisation potential of 9.0 eV estimated in this laboratory for $(EtO)_2P(O)NHC(O)Ph$.[61] The ionisation potential estimated[61] was the only data available for phosphoryl compounds. Under these conditions one of the major fragments observed results from expulsion of the metaphosphate species, $ClCH_2CH_2NH\text{-}PO_2$, accompanied by phenyl group migration from oxygen to nitrogen yielding $PhNHMe]^{+\cdot}$, m/e 107, rel. intensity 72%. It seems therefore that reaction 61 requires development of the radical cation centre at the nitrogen atom and involves O → N migration similar to other migrations to an electron deficient nitrogen atom (Eq. 62).[22c]



(18')

$$\longrightarrow \quad R''R'NR\,]^{+\cdot} \quad + \quad YPO_2 \qquad (62)$$

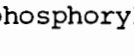
*It has been shown[60] that the elimination of ethanol from diethylphosphate to produce ethyl metaphosphate [$(EtO)_2PO_2H \rightleftharpoons EtO\text{-}PO_2 + EtOH$] is characterised by a free energy of $\Delta G° \approx 30$ kcal mol^{-1} and an equilibrium constant of $K \approx 10^{-20}$.

P-N bond cleavage accompanied by O → N migration, although found for twenty-five of the amidoesters was not observed for the remaining fourteen theoretically capable of transferring the ester R group to the departing nitrogen atom. The main reason for the absence of fragmentation according to pathway (c) (Scheme 8) is that some other preferred collapse of the molecular ion, must occur faster than reaction 61. One of the major reactions of this type is the loss of alkyl radical from those substrates which are substituted by an alkyl group higher than methyl either at nitrogen (18Ab-d), (18Bc,d,f) or at the N-phenyl ring (18Aj,k). Other specific fragmentations likely to be responsible for quenching the formation of the N-substituted amine radical ion are: the loss of $NO_2^{\bullet}$ (18Ao), $Me^{\bullet}$ from a *p*-MeO group (18An) or $CH_2Cl^{\bullet}$ (17b). In three cases the failure to observe products (see Eq. 61) sheds some light on the structural requirements of this rearrangement. Neither tertiary phosphoramidates $(MeO)_2P(O)NMe_2$ (21) or $(PhO)_2P(O)NMe_2$ (18Bi) produce, on fragmentation, the radical ions of the corresponding tertiary amines (trimethyl and phenyldimethyl, respectively). This result is attributed to the steric effects of the two N-methyl groups which would hinder the approach of a migrating fragment in the transition state. This conclusion was confirmed by comparison of the mass spectra of the two isomeric N-(dimethylphenyl)phosphoramidates (18Al) and (18Am). The 3,4-dimethyl derivative (18Al) yields in its spectrum two peaks (m/e 135, 134; total rel. intensity 19%) resulting from the P-N bond cleavage accompanied by O → N methyl migration and followed by the loss of hydrogen from the amine radical ion formed (Eq. 63).

$$\underline{18Al} \xrightarrow{-e^{\ominus}} (MeO)_2P(O)NH\text{-}C_6H_3Me_2\text{-}3,4\ ]^{+\bullet} \longrightarrow \tag{63}$$

$$MeO\text{-}PO_2 + \underset{m/e\ 135}{3,4\text{-}Me_2C_6H_3NHMe\ ]^{+\bullet}} \xrightarrow{-H^{\bullet}} \underset{m/e\ 134}{3,4\text{-}Me_2C_6H_3NHCH_2\ ]^{+}}$$

The fragment at m/e 135 is absent in the spectrum of the 2,6-dimethylphenyl derivative (18Am); the related fragment m/e 134 is observed but occurs with very low intensity (≤ 5%). Since any electronic effects operating in (18Al) and (18Am) should, to a first approximation, be the same, the observed difference in fragmentation behaviour must stem from the steric hindrance of the two *ortho*-methyl groups in (18Am) which inhibit migration of another methyl group from the oxygen to the nitrogen atom. Kinetic measurements of the hydrolysis of N-aryl-substituted dimethylphosphoramidates, $(MeO)_2P(O)NHAr$, showed that the relative reactivities of the 3,4-dimethyl substituted (Ar = $3,4\text{-}Me_2C_6H_3$), unsubstituted (Ar = Ph) and 2,6-dimethyl substituted (Ar = $2,6\text{-}Me_2C_6H_3$) compounds were 1.63, 1.00 and 0.26 respectively.[25] The low reactivity of the *ortho*-disubstituted substrate was explained in terms of steric hindrance to the approach of water to the crowded amide function.

The mass spectrum of the phosphorylated ethylenimine $(MeO)_2P(O)N$  (22a) indicates that the tertiary nitrogen atom in this compound is more electron deficient than in $(MeO)_2P(O)NMe_2$ (21), as migration to the nitrogen atom, which occurs to a limited extent in (22a) [m/e 57 (4%)] is absent in (21). The difference in electron density at the nitrogen atom in (21) as compared with (22a) and the effect of this on the chemical behaviour of these compounds is discussed in Chapter 5.

Equation 62 implies the migration of group R, with its bonding electrons, to the electrophilic nitrogen atom. An examination of the electronic effects of substituents on the rearrangement might provide evidence for this mechanism. For N-aryl dimethylphosphoramidates the fragmentation involves, according to Eq. 62, migration of the electron-rich methyl group to the nitrogen atom. The electrophilicity of the nitrogen atom should be modified by the polar effects of ring substituents. Following the elegant approach applied by

Djerassi and Brown[21] to rearrangements in organic carbonates, a linear free-energy relationship was developed for the fragmentation shown in Eq. 64.

$$(MeO)_2P(O)NHAr\ ]^{+\cdot} \xrightarrow{-\ MeO\text{-}PO_2} ArNHMe\ ]^{+\cdot} \xrightarrow{-\ H^{\cdot}} ArNHCH_2\ ]^{+} \qquad (64)$$

M $\qquad$ F_1 $\qquad$ F_2

Since the loss of hydrogen from radical ions F_1 to give ions F_2 is a very facile reaction, the abundance of both the F_1 and F_2 fragments was taken as a measure of the efficiency of reaction 62. The function Z (see Eq. 65),

$$Z = \Sigma F/M \qquad (65)$$

where ΣF is the abundance of ions F_1 and F_2 and M is the abundance of the molecular ion, was calculated. In order to minimise the effect of competitive fragmentations on the value of Z, the method was applied only to selected substrates such as unsubstituted (18Ae, Ar = Ph), three of the methyl-substituted (18Ag, Ar = 3-MeC_6H_4), (18Ah, Ar = 4-MeC_6H_4), (18Al, Ar = 3,4-Me_2-C_6H_3) and fluoro (18Ar, Ar = 4-FC_6H_4) derivatives. For these closely-related, sterically-unhindered substrates, any competing fragmentations (loss of MeOH, simple P-N cleavage, *etc.*) should occur to a similar extent and the value of Z should be directly related to the degree of electron release to the positively charged nitrogen atom by ring substituents. Other ring-substituted phosphoric anilides could not be included in the calculation of Z because of predominant fragmentations involving ring substituents (higher alkyl groups, methoxy, phenoxy and nitro groups), which reduced the relative abundance of the ions F_1 and F_2. Estimated values of Z were then correlated with the substituent constants σ^+ according to the linear free-energy relationship (Eq. 66) which permits kinetic evaluation of mass spectra.[21]

$$\log Z_x = \rho\sigma_x^+ \qquad (66)$$

It should be noted that the charge on the molecular ion (18') formed from (18) by electron impact may be located on the electron deficient nitrogen atom (see Eq. 62). Since three of the substrates (18Ah), (18Al) and (18Ar) have the electron deficient centre in direct conjugation with an electron-donating substituent, the substituent constants, σ^+, were used for the linear free-energy relationship (Eq. 66).[62] The results derived from Eq. 65 are presented in Table 11 and the linear free-energy relationship is illustrated in Figure 14.

Table 11 Z values (Eq. 65) for the fragmentation of N-aryl dimethylphosphoramidates

Compound	Ring Substituent X in Ar	σ_x [a]	Z_x [b]	No. of scans
(18Ae)	H	0.00	0.62 ± 0.08	12
(18Ag)	3-Me	-0.07	0.42 ± 0.07	8
(18Ar)	4-F	-0.07	0.34 ± 0.04	8
(18Ah)	4-Me	-0.31	0.29 ± 0.04	9
(18Al)	3,4-Me_2	-0.38	0.12 ± 0.01	10

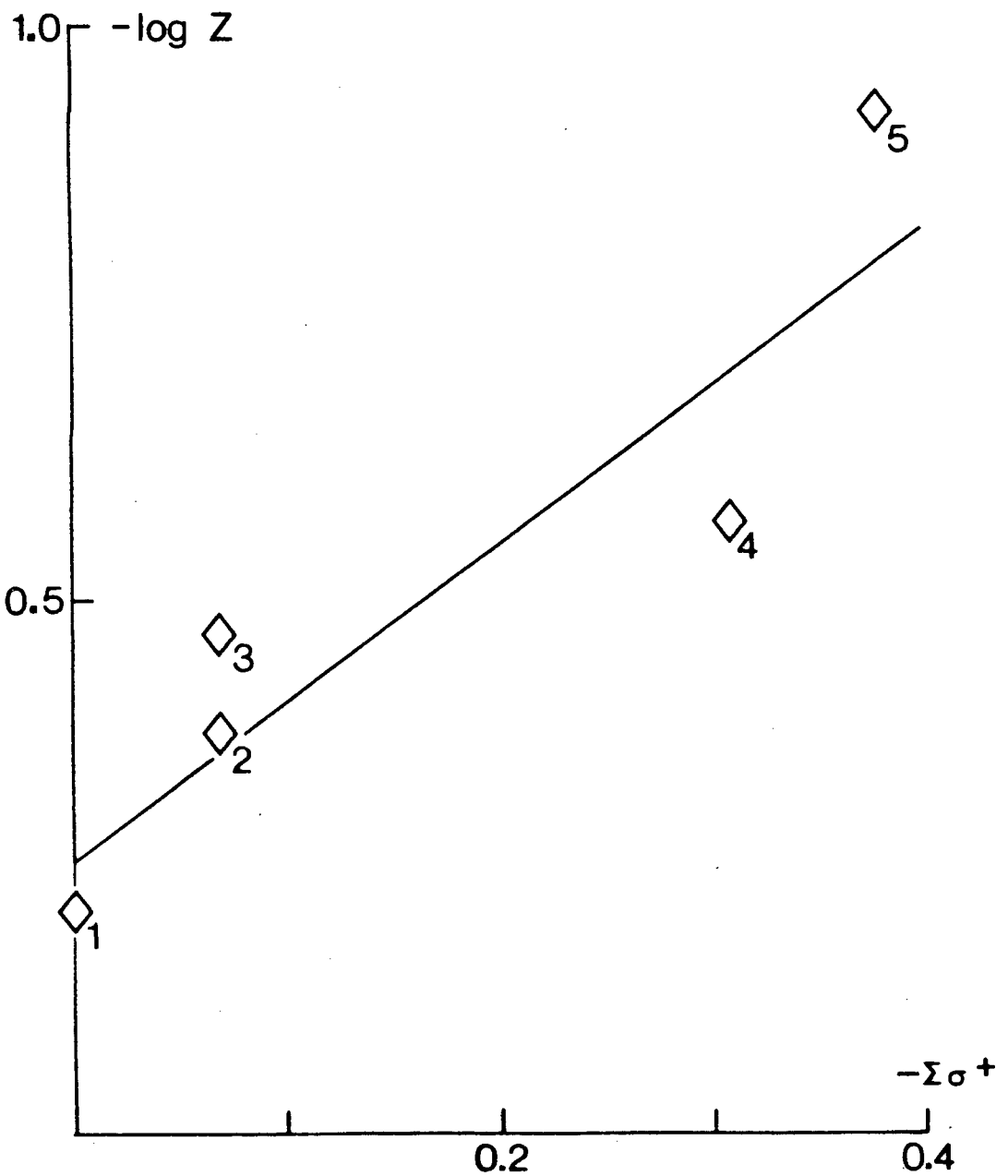
a. Taken from Ref. 48, Chapter 3.5

b. Average from number of scans given.

Although the linearity of the plot is rather poor ($r = 0.895$),* the trend is obvious and indicates that, in agreement with the proposed mechanism, electron-releasing substituents in the aromatic amine moiety inhibit migration of R to the nitrogen atom. The reaction constant $\rho = 1.4$ obtained for compounds (18A)

* Similar correlation obtained by Djerassi[21] also showed considerable scatter with a standard deviation of the slope of 27%.

Figure 14 Linear free-energy relationship $\log Z_x = \rho\sigma_x^+$



1 (18Ae), 2 (18Ag), 3 (18Ar), 4 (18Ah), 5 (18Al)

is higher than that (ρ = 0.67) reported by Djerassi[21] for rearrangement in organic carbonates. The greater sensitivity observed for the phosphoramidates most probably results from less electron-density at the nitrogen atom in the $P(O)N]^{+\cdot}$ function relative to the carbonate system.

In $(PhO)_2P(O)NHMe$ (18Ba) the rearrangement outlined in Eq. 62 and 64 should give rise to the ions $PhNHMe]^{+\cdot}$ (m/e 107) and $PhNHCH_2]^{+}$ (m/e 106). These ions were observed in the spectrum of (18Ba) and exact mass measurements confirmed their structures. The results are shown in Table 12.

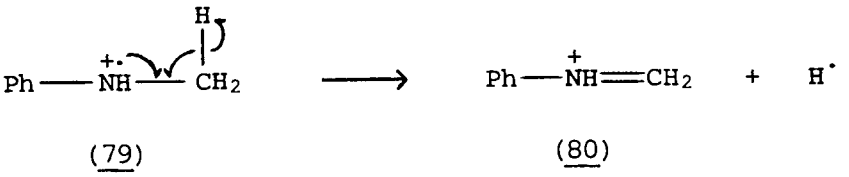
Table 12 Exact mass measurements for (18Ba)

	$PhNHMe]^{+\cdot}$	$PhNHCH_2]^{+}$
	C_7H_9N	C_7H_8N
exact mass observed	107.0706	106.0619
exact mass calculated[1]	107.0733	106.0655

1 Nuclidic mass taken from Ref. 53, p. 275

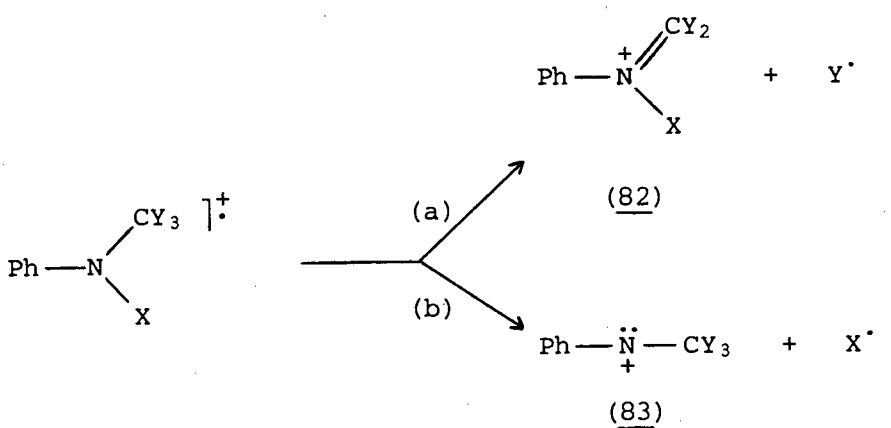
4.2.4 FRAGMENTATION PATHWAYS OF SECONDARY AMINE RADICAL IONS

The fragmentation pathways of secondary amine radical ions were examined. In all cases, the secondary amine radical ion, $R''R'NH]^{+\cdot}$, produced either by pathway (b) or (c) (Scheme 8), was accompanied by a strong $(M-1)^{+}$ peak, resulting from loss of a hydrogen atom (Eq. 60). The general occurrence of this fragmentation pathway prompted further investigation. Thus N-methylaniline (79) and its analogues were used as model compounds in order to shed some light on the mechanism of this reaction. For the radical ion of (79) the most obvious way of losing hydrogen is α-cleavage,[57] yielding the stable iminium ion (80) (Eq. 67).



(79) (80) (67)

Reaction 67 was easily verified by labelling experiments. The mass spectra of N-methylaniline (79), N-deuteratedmethylaniline (79a) and N-(trideutero-methyl)aniline (79b) as well as N,N-dimethylaniline (81) were recorded. In each of these substrates homolytic bond cleavage of the molecular ion can involve either the C-Y bond [Scheme 9 pathway (a)] or the N-X bond [Scheme 9 pathway (b)], giving rise to one of the ions (82) or (83).



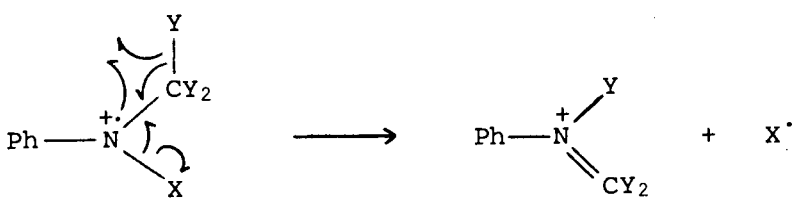
(82) (83)

(79) X = Y = H
(79a) X = D, Y = H
(79b) X = H, Y = D
(81) X = Me, Y = H

Scheme 9

The mass spectrum of the reference substrate (79) recorded over the temperature range 185 - 220°C, showed the $(M-1)^+$ fragment at m/e = 106 as the base peak, together with the molecular ion; (m/e = 107, rel. int. *ca.* 80%). For the molecular ion derived from (79a) m/e 108, loss of D$^\cdot$ (m/e = 106, base peak) was slightly preferred over loss of H$^\cdot$ (m/e = 107). After correcting for statistical factors the intensity ratio of fragments

m/e = 106 to m/e = 107 was *ca.* 3.6:1. When the location of the H and D atoms was reversed as in (79b), loss of $H^{\cdot}$ and $D^{\cdot}$ occurred to approximately the same extent. Although the $(M-2)^{+}$ peak (m/e = 108) was formed from (79b) as the base peak, after statistical correction its intensity relative to the $(M-1)^{+}$ peak (loss of $H^{\cdot}$) was 0.9:1. Similarly in the spectrum of N,N-dimethylaniline (81), recorded over the temperature range 180 - 220°C, the ions m/e = 120 (loss of $H^{\cdot}$) and m/e = 106 (loss of $Me^{\cdot}$) gave the most abundant peaks which were of almost the same intensity. In conclusion it was found that the two fragmentations indicated in Scheme 9 (loss of $Y^{\cdot}$ or $X^{\cdot}$) occurred with very low intramolecular selectivity. Since the stabilities of the two ions [iminium (82) *vs.* nitrenium (83)] formed must be different it is proposed that pathway (b) in fact involves rearrangement yielding another iminium ion (84) as shown in Eq. 68.

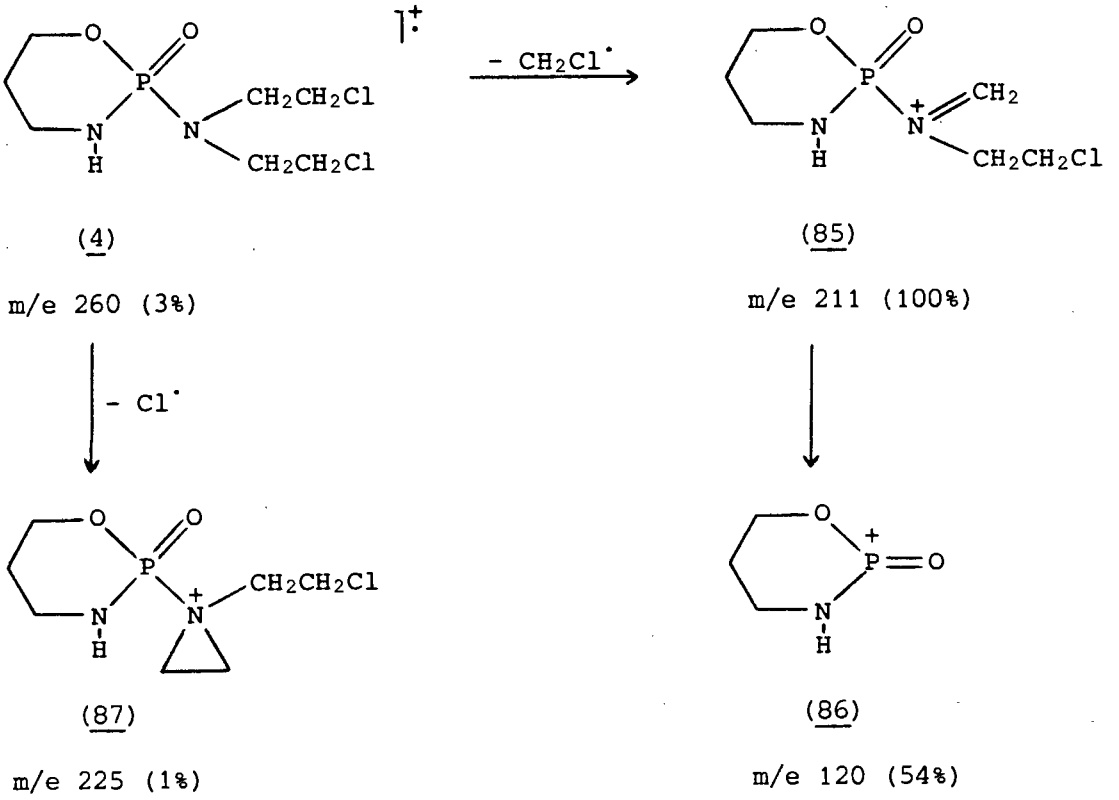


(68)

(84)

4.2.5 FRAGMENTATION PATHWAYS OF PHOSPHORAMIDATES CONTAINING THE N-(β-CHLOROETHYL) GROUP

The electron ionisation spectrum of cyclophosphamide (4) was published recently[23] and the most important fragmentation pathways are shown in Scheme 10.



(4) m/e 260 (3%)

(85) m/e 211 (100%)

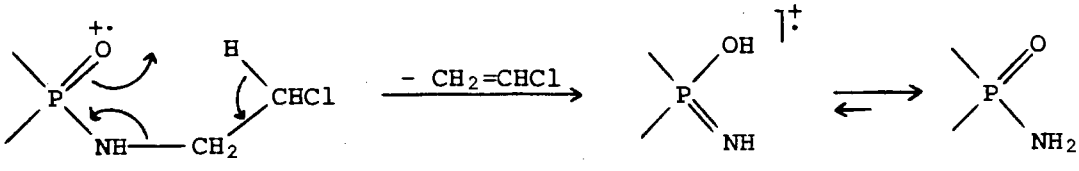
(87) m/e 225 (1%)

(86) m/e 120 (54%)

Scheme 10

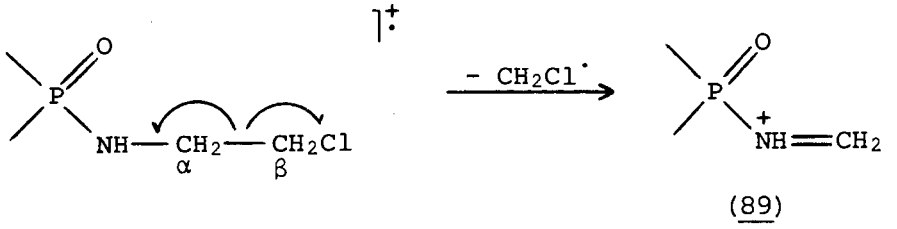
Six members (15a,b), (16a,b,c,d) of the series investigated here contain the N-(β-chloroethyl) group responsible for the cytostatic alkylating activity of phosphoramide mustards.[7] The mass spectra were examined and compared with that reported for cyclophosphamide.

One of the characteristic fragmentations observed for (15a,b) and (16a,d) is an extension of the McLafferty rearrangement, involving the elimination of vinyl chloride and the formation of the primary phosphoramidate, (88), probably *via* its tautomeric form (88a) (see Eq. 69).



(88a) (88) (69)

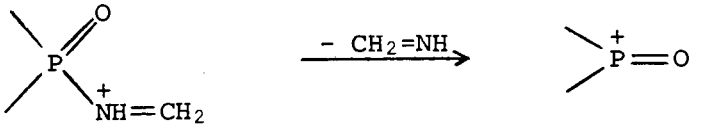
The most common fragmentation observed for all six substrates, supported by metastable peaks for (15b) and (16a-c), was cleavage of the $C_\alpha - C_\beta$ bond (Eq. 70).



(70)

(89)

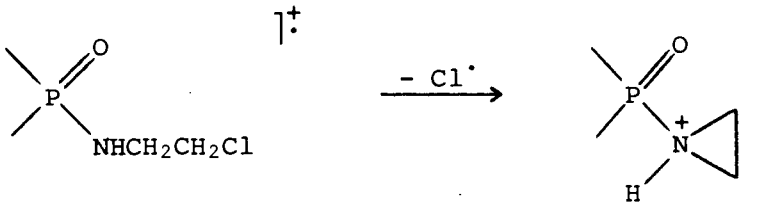
The resonance-stabilised ion (89) was one of the major peaks in this series of spectra and most secondary fragmentations originated from this ion. $C_\alpha - C_\beta$ bond cleavage also gave rise to the most abundant ion (85) in the spectrum of cyclophosphamide. One of the interesting fragmentations of (89), supported by metastable peaks for all substrates except (16b), where elimination of phenol is a competing pathway, is loss of methylenimine to give the phosphorylium ion (90) (Eq. 71).



(71)

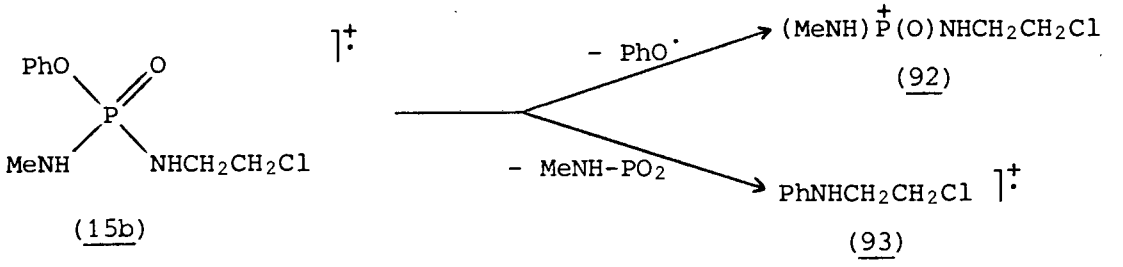
(89) (90)

Thus in this class of compounds the phosphorylium ion (90) was not formed by direct P-N bond cleavage of the molecular ion, but after initial $C_\alpha - C_\beta$ bond fission of the β-chloroethyl group. The phosphorylium ion, (86), observed in the spectrum of cyclophosphamide (4), was also formed *via* (85) and not directly from the molecular ion (see Scheme 10). As observed for (4), the compounds (15) and (16) all eliminated $Cl^\cdot$ yielding the ions (91) (Eq. 72).



(91) (72)

In the spectrum of (15b) the fragment at m/e 155 could either be produced by a direct fission process yielding (92) or by migration of a phenyl group from oxygen to nitrogen yielding (93) (see Eq. 73).



(15b) (92) (93) (73)

The exact mass of the fragment at m/e 155 was determined in order to assign its structure. The results are presented in Table 13.

Table 13 Exact mass measurements for m/e 155 in (15b)

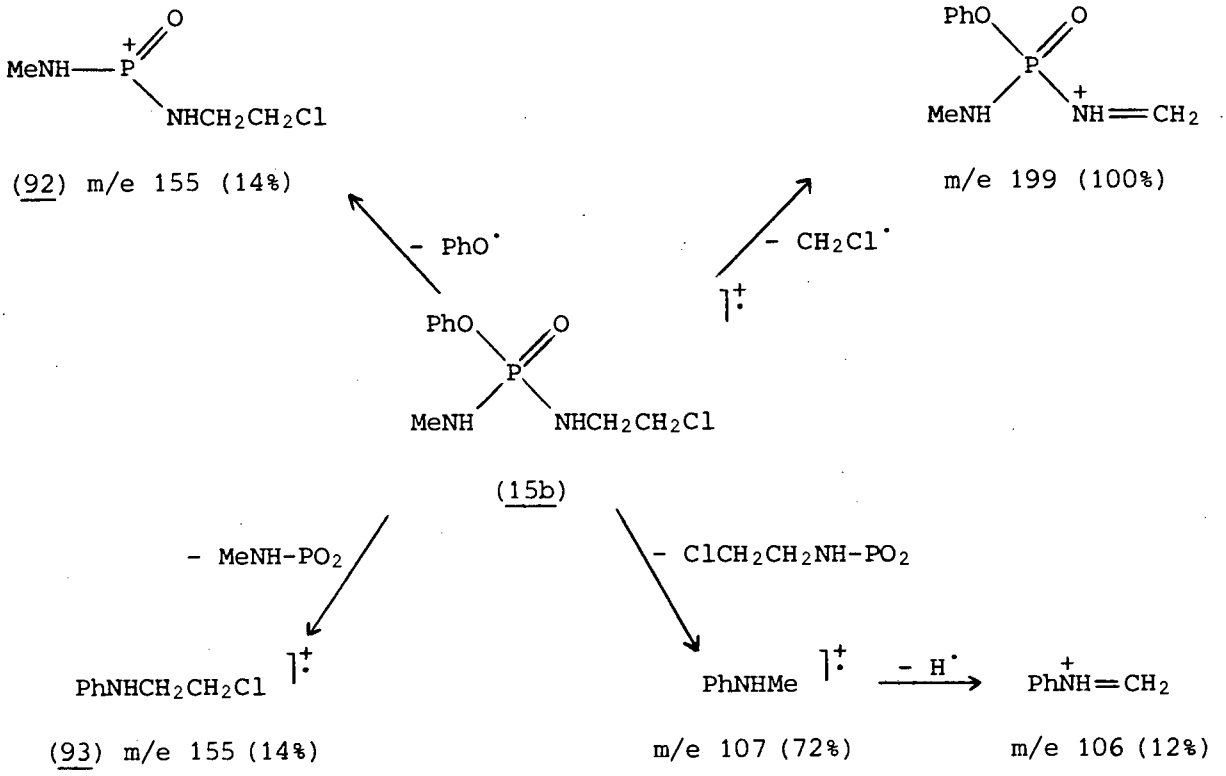
	$(MeNH)\overset{+}{P}(O)NHCH_2CH_2Cl$ (92)	$PhNHCH_2CH_2Cl]^{+\cdot}$ (93)
	$C_3H_9ClN_2OP$	$C_8H_{10}ClN$
exact mass observed	155.0196	155.0526
exact mass calculated[1]	155.0140	155.0520

1. Nuclidic masses taken from Ref. 53, p. 275.

These results show that both (92) and (93) are formed from (15b) under conditions of electron impact. It should be noted that the ester R group migration from oxygen to the nitrogen atom of the N-(β-chloroethyl) group occurred in (15a), (16a) and (16b) to a limited extent (rel. intensities of the peaks observed ranged from 2 - 5%).

4.2.6 FRAGMENTATION PATHWAYS OF (PhO)(MeNH)P(O)NHCH$_2$CH$_2$Cl (15b) AT LOW ENERGY

As the energy of the electron beam is lowered the potential energy distribution of the molecular ion becomes weighted to lower energies. Thus ions formed from reactions requiring more energy (whether produced in one or more steps from the molecular ion) diminish in intensity or disappear altogether.[63] At low beam energies therefore only primary reactions of low activation energy occur and consecutive decompositions are minimised. Scheme 11 outlines the fragmentations observed when the spectrum of (15b) was recorded at low energy (11 eV), which is just above the ionisation energy estimated in this laboratory for (EtO)$_2$P(O)NHC(O)Ph.[61]



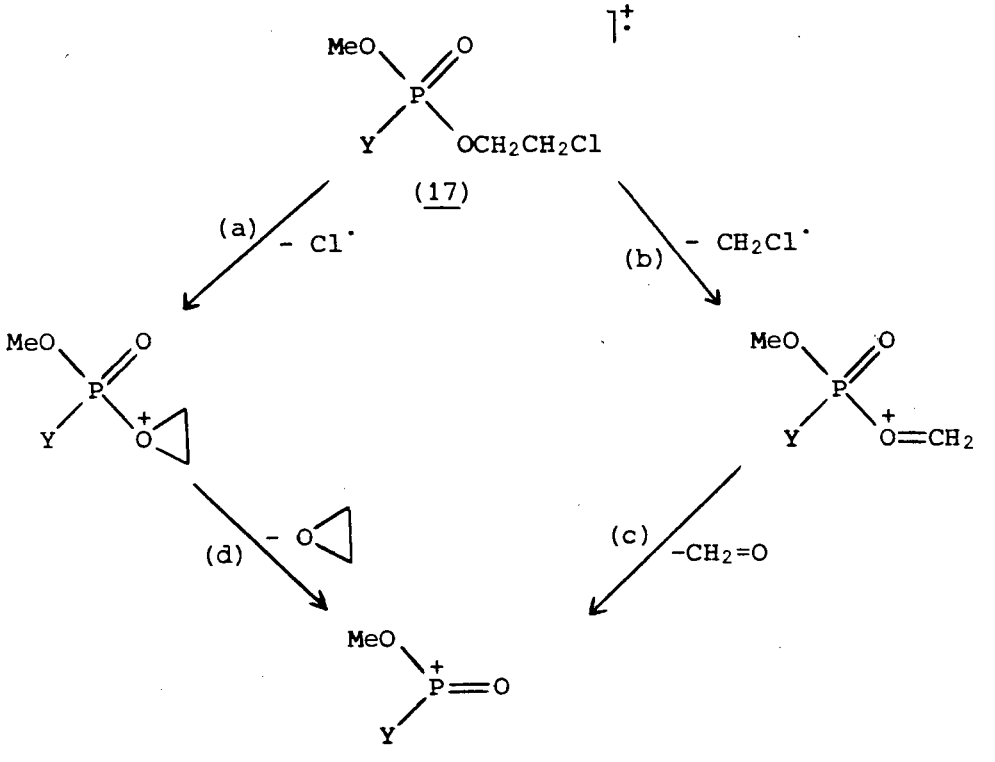
Scheme 11

The migration of an ester group from oxygen to nitrogen (discussed in Chapter 4.2.3) is clearly a facile process requiring low activation energy. In

compound (15b) the phenyl group migrations occurred at low beam energy giving the radical ions $PhNHMe]^{+\cdot}$ and $PhNHCH_2CH_2Cl]^{+\cdot}$, the former being the second most abundant peak in the spectrum. It is interesting to note that the only mode of P-N bond cleavage occurring at low energy is the pathway involving migration of a phenyl group from the oxygen to the nitrogen atoms. No clear explanation for this observation is available at present.

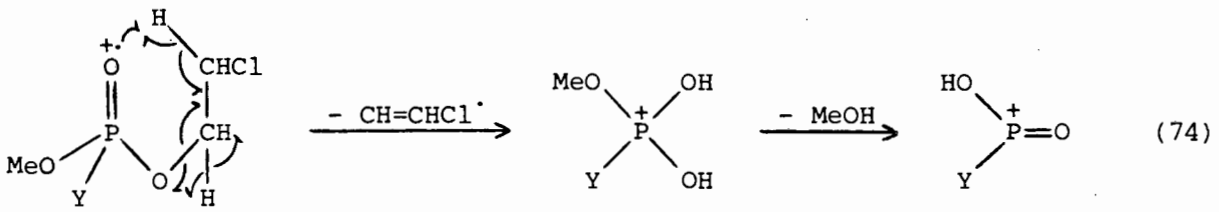
4.2.7 FRAGMENTATION PATHWAYS OF ORGANOPHOSPHORUS COMPOUNDS CONTAINING THE O-(β-CHLOROETHYL) GROUP

The mass spectra of compounds (17) were recorded and a few of the most important fragmentation pathways are outlined in Scheme 12.



Scheme 12

Pathways similar to (a), (b) and (c) in Scheme 12 were also observed in the spectra of the nitrogen analogues (15a) and (16a). Pathway (d), involving elimination of ethylene oxide was, however, unique to (17) and was confirmed by a metastable peak for both (17a) and (17b). The phosphorylium ion (94), formed *via* the two fragmentation pathways (c) and (d), was the base peak in both spectra. These compounds also eliminated radical vinyl chloride yielding the quasi-phosphonium ion (95) which then expelled methanol to give the phosphorylium ion (96) (Eq. 74).



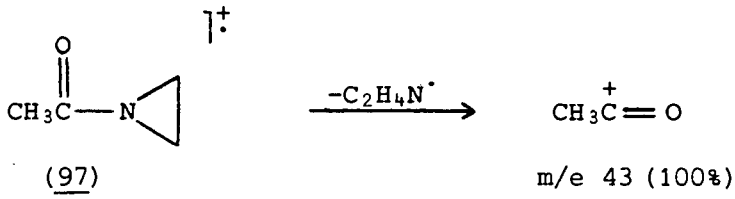
(17) (95) (96) (74)

It is of interest to note that whereas compounds (15a) and (16a) eliminated neutral vinyl chloride *via* a McLafferty rearrangement (Eq. 69), compounds (17) expelled the radical $C_2H_2Cl^{\cdot}$ by a double hydrogen rearrangement (Eq. 74). This double hydrogen rearrangement has been observed before in radical ions containing the $\rangle P(O)OEt$ moiety.[16, 50]

4.2.8 FRAGMENTATION PATHWAYS OF N-PHOSPHORYLATED ETHYLENIMINES

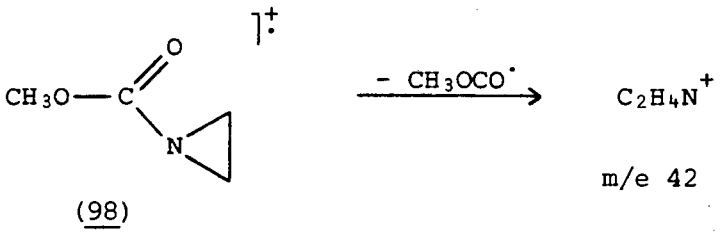
The mass spectra of phosphoramidates $X_2P(O)N\triangleleft$ (22) were also examined. Some of the fragmentations, *viz.* migration of a hydrogen atom and release of neutral phosphite, as well as methyl group migration from oxygen to nitrogen, have been discussed earlier (see Chapter 4.2.2 and 4.2.3).

Simple P-N bond cleavage yielding a phosphorylium ion, $X_2\overset{+}{P}{=}O$, parallels the behaviour of N-acetylethylenimine (97) (Eq. 75).[64]



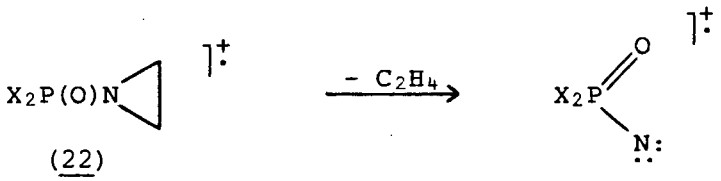
(97) m/e 43 (100%) (75)

P-N bond cleavage also occurs, yielding an amino cation, $C_2H_4N^+$, as a relatively intense peak. This is the base peak in the spectrum of $(MeO)_2P(O)N$ (22a). In this respect (22a) resembles the carbamate (98). The fragment $C_2H_4N^+$ (m/e 42) formed in one step from the molecular ion, is the base peak in the spectrum of (98) (Eq. 76).[64]



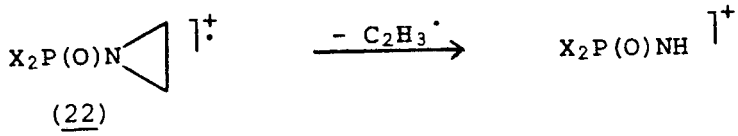
(98) m/e 42 (76)

It has been observed that under conditions of electron impact ethylenimine eliminates neutral ethylene.[65] This fragmentation pathway has been observed in the present work for the phosphorylated ethylenimines (22) as well and was confirmed by metastable peaks for (22a,b,c) (Eq. 77).



(22) (77)

Another fragmentation pathway involving the nitrogen-containing three-membered ring was elimination of the radical $C_2H_3^{\cdot}$ as shown in Eq. 78 and supported by metastable peaks for (22a,c).



(22) (78)

In conclusion, the mass spectra of the phosphoramidates (18) demonstrate that the molecular ion (18') produced by electron impact has a complex fragmentation pattern which involves both the amide and the ester functions, P-N bond cleavage often being accompanied by hydrogen or skeletal rearrangements.

The mass spectra of the following compounds were recorded and are discussed in Chapter 4.

$X(MeNH)P(O)NHCH_2CH_2Cl$ (15)

a: X = MeO

b: X = PhO

$X_2P(O)NHCH_2CH_2Cl$ (16)

a: X = MeO

b: X = PhO

c: X = Et

d: X = Ph

$Y(MeO)P(O)OCH_2CH_2Cl$ (17)

a: Y = MeO

b: Y = MeNH

$(RO)_2P(O)NR'R''$ (18A)

R = Me; R' = H

a: R'' = Me

b: R'' = Et

c: R'' = ^{i}Pr

d: R'' = ^{t}Bu

e: R'' = Ph

f: R'' = $2\text{-}MeC_6H_4$

g: R'' = $3\text{-}MeC_6H_4$

h: R'' = $4\text{-}MeC_6H_4$

i: R'' = $2\text{-}EtC_6H_4$

j: R'' = $4\text{-}EtC_6H_4$

k: R'' = $4\text{-}nBuC_6H_4$

l: R'' = $3,4\text{-}Me_2C_6H_3$

m: R'' = $2,6\text{-}Me_2C_6H_3$

n: R'' = $4\text{-}MeOC_6H_4$

o: R'' = $3\text{-}NO_2C_6H_4$

p: R'' = $4\text{-}PhOC_6H_4$

q: R'' = $4\text{-}PhC_6H_4$

r: R'' = $4\text{-}FC_6H_4$

(18A) R = CD_3; R' = H

s: R'' = Ph

t: R'' = $4\text{-}MeC_6H_4$

R = Et; R' = H

u: R'' = Me

v: R'' = Ph

R = Me; R' = D

w: R'' = Ph

$(PhO)_2P(O)NR'R''$ (18B)

R' = H

a: R'' = Me

b: R'' = Et

c: R'' = ^{i}Pr

d: R'' = ^{t}Bu

e: R'' = CH_2Ph

f: R'' = CH(Me)Ph

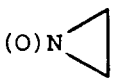
g: R'' = $CH_2C_6H_4\text{-}4\text{-}Me$

h: R'' = Ph

R' = Me

i: R'' = Me

$(MeO)_2P(O)NMe_2$ (21)

$X_2P(O)N$  (22)

a: X = MeO

b: X = Et

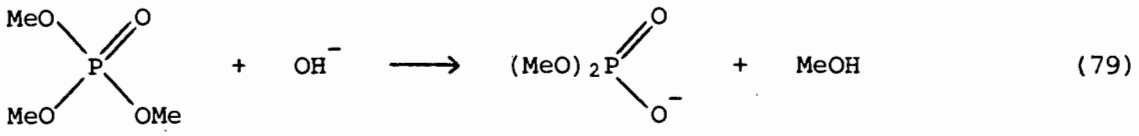
c: X = Ph

CHAPTER FIVE

NUCLEOPHILIC CLEAVAGE OF THE ESTER AND AMIDE BONDS IN PHOSPHORAMIDATES

5.1 INTRODUCTION

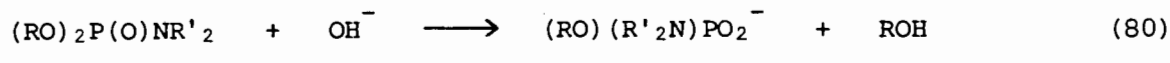
It has been shown that alkaline hydrolysis of the phosphate ester bond in trimethyl phosphate (99) occurs with P-O bond fission (Eq. 79).[66]



(79)

(99)

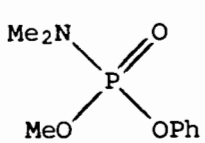
Because of the difference in the nucleofugality of the OR and NR'_2 groups, the basic hydrolysis of $(RO)_2P(O)NR'_2$ (100) resulted in ester bond cleavage only. No amide (P-N) bond cleavage was observed (Eq. 80).[67]



(80)

(100)

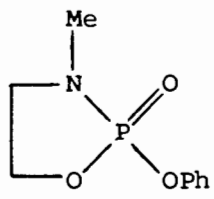
The only notable exception to the reaction shown in Eq. 80 was for the phosphoramidates in which the nitrogen and an oxygen atom were constrained in a five-membered ring; in these systems P-N bond cleavage was found to compete with cleavage of the P-O bond.[28] In that work the alkaline hydrolysis of the aryl alkyl phosphoramidate (101) and its cyclic analogue (102) was investigated and the results obtained are shown below:



(101)

100% P - OPh bond cleavage

at 25 °C $k_2 = 6.85 \times 10^{-6}$ ℓ mol^{-1} s^{-1}



(102)

91% P - OPh bond cleavage

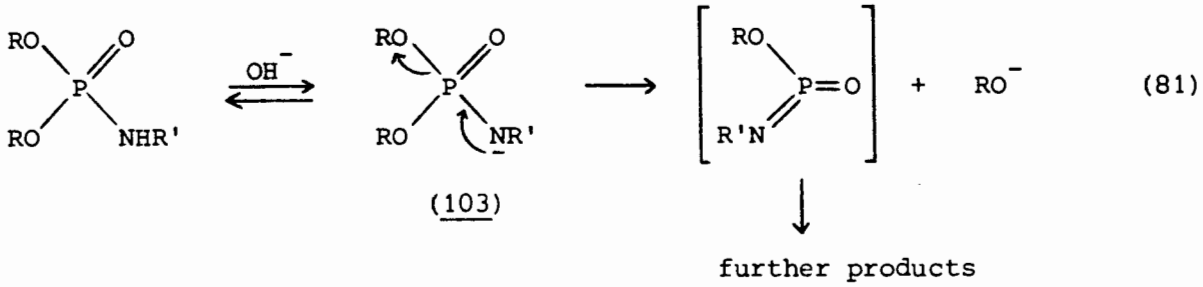
5% P - N bond cleavage

4% P - OCH_2 bond cleavage

at 25 °C $k_2 = 1.24 \times 10^{-1}$ ℓ mol^{-1} s^{-1}

The increase in the rate of reaction of (102) relative to (101) by a factor of *ca.* 1.8 x 10^4 was ascribed to the relief of ring strain during hydrolysis of the cyclic ester.[28]

The R'_2N group in $(RO)_2P(O)NR'_2$ (100) is resistant to nucleophilic substitution. It also strongly deactivates the ester functions by donating electrons to the phosphoryl centre.[68] This deactivation by the tertiary NR'_2 group in (100) is absent in secondary phosphoramidates as these are capable of reacting *via* the reactive conjugate base intermediate (103) (Eq. 81).[69]

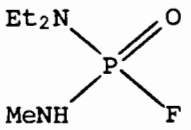


(81)

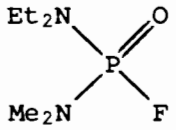
(103)

further products

The base-catalysed hydrolysis of the secondary phosphoramidate (104) has been found to be almost 10^4 times faster than that of its fully-alkylated analogue (105). The reaction occurred *via* the conjugate base intermediate of (104).[69]

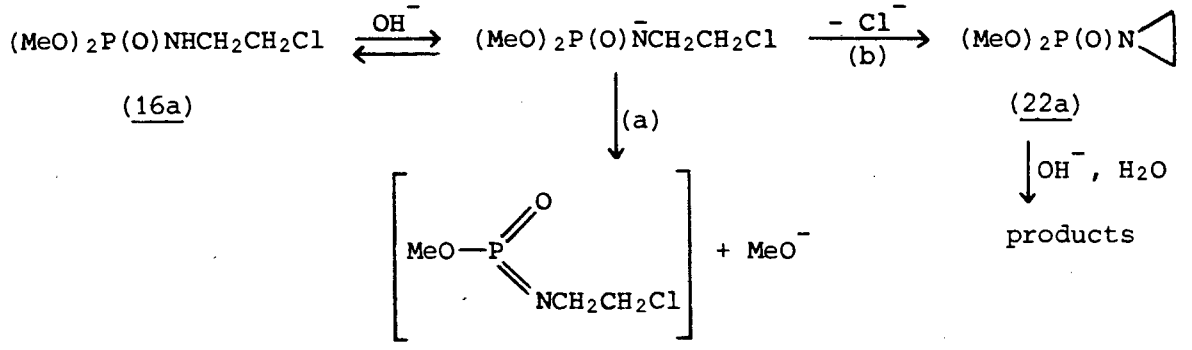


(104)



(105)

The nucleophilic reactivity of the N-(β-chloroethyl) phosphoramidates $X_2P(O)NHCH_2CH_2Cl$ (16) and their conversion to N-phosphorylated ethylenimines was discussed in Chapter 3.2.1. In the present work the alkaline hydrolysis of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) and $(MeO)_2P(O)N$  (22a) was investigated. The aim of this study was two-fold: firstly, the hydrolysis of (16a) was of interest since the reaction might proceed *via* either of the two independent pathways, or both, as shown in Scheme 13.



Scheme 13

Pathway (a) can be compared with the hydrolysis of the secondary phosphoramidate $(MeO)_2P(O)NHMe$ (18Aa), while pathway (b) involves initial ring closure analogous to the reactions discussed in Chapter 3.2.1. Secondly, the reactivity of (22a) was investigated and compared with that of $(MeO)_2P(O)NMe_2$ (21) in order to evaluate the effect of the ethylenimine group on the rate of nucleophilic displacement at phosphorus.

The relative reactivity of (21) and (22a) towards other reagents such as water (a poor nucleophile) and the more powerful nucleophile, MeO^- was also investigated. The fluoride ion has been shown[70] to activate nucleophilic displacement at tetrahedral phosphorus. For example, in the absence of fluoride, the reaction of 2-chloro-2-oxo-1,3,2-dioxaphosphorinane with alcohols or phenols was very slow (two weeks for reaction with 2-propanol). When CsF was added, however, the reaction went to completion within several hours.[70] Therefore the relative reactivity of (21) and (22a) was also investigated in water containing NaF in order to determine whether nucleophilic substitution in these substrates is activated by the presence of the fluoride ion.

5.2 RESULTS AND DISCUSSION

5.2.1 P-O BOND CLEAVAGE

The rates of alkaline hydrolysis for substrates having the general formula $(MeO)_2P(O)Y$ (106) (see Eq. 82) were determined and the results are presented in Table 14.

$$(MeO)_2P(O)Y \xrightarrow[k_2]{OD^-,\ D_2O} Y(MeO)PO_2^- + MeOD \qquad (82)$$

(106)

Table 14 Rates of alkaline hydrolysis of $(MeO)_2P(O)Y$ (106).

$[OD^-] = 1.68\ M$ [substrate] = 0.31 M

Substrate	Temp., °C	Y	$10^4 \times k_2$ (ℓ mol^{-1} s^{-1})[a]	k_{rel}
$(MeO)_3PO$ (99)	31	OMe	1.0[b]	1
$(MeO)_2P(O)NMe_2$ (21)	31	NMe_2	0.0040[b]	4×10^{-3}
$(MeO)_2P(O)NMe_2$ (21)	25	NMe_2	0.0027	-
$(MeO)_2P(O)NHMe$ (18Aa)	25	NHMe	0.4	0.6[c]
$(MeO)_2P(O)N$  (22a)	31	N 	2.9	2.9

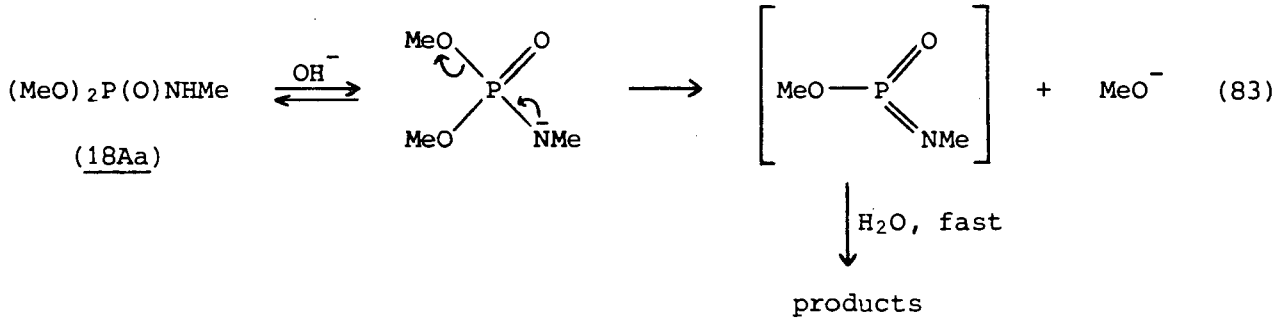
a. Statistically corrected for the number of potential methoxide leaving groups.

b. Lit.[68] $k_2 = 1.1 \times 10^{-4}$ ℓ mol^{-1} s^{-1} for (99) and 4.2×10^{-7} ℓ mol^{-1} s^{-1} for (21)

c. Calculated by stepwise comparison with the rate of hydrolysis of (21) at 25 °C.

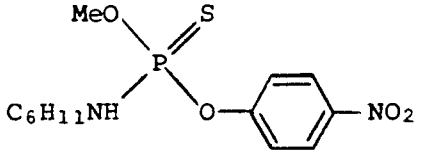
These results confirm that the dialkylamino group deactivates the phosphate bond towards cleavage by nucleophiles as has been observed before[68] in comparing compounds (21) and (99). The 250-fold decrease in reactivity of (21) relative

to (99) is a measure of the electron-releasing effect of the NMe_2 group in (21) relative to the OMe group in the triester (99). The P-O bond in the amide (18Aa) was, however, cleaved at a rate comparable to that for the reference compound (99). The considerable difference in reactivity of the P-O bond observed for the tertiary and secondary phosphoramidates [k_{P-O} (18Aa)/k_{P-O} (21) = 150] suggests the participation of an E1cb mechanism[69] in the hydrolysis of (18Aa) as shown in Eq. 83.

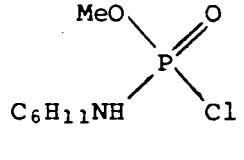


(83)

Similar activation has previously been reported for P-OAr and P-Cl bond cleavage in (107) and (108) respectively.[69]



(107)



(108)

It is interesting to note that this activation also occurred in (18Aa) despite the fact that this phosphoramidate has a poorer leaving group (OMe) than those of (107) or (108).

A comparison of the rates of P-O bond cleavage in the two tertiary phosphoramidates $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_2P(O)N$ (22a) shows that a change from the N,N-dimethylamino group to the N-ethylene group has a powerful effect on the reactivity of the adjacent phosphate ester linkage, [k_{P-O} (22a)/k_{P-O} (21) = 725]. The P-OMe bond in the ethylenimine derivative

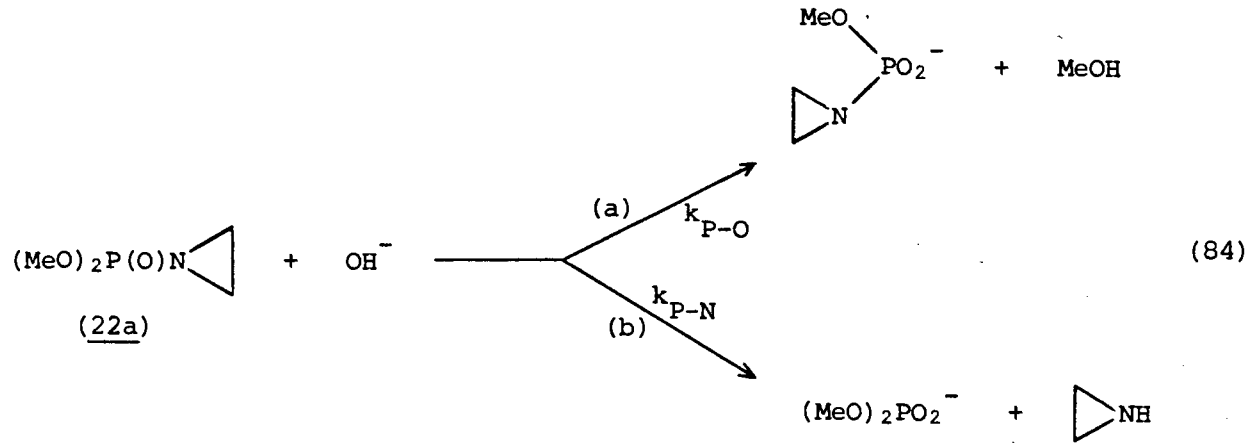
(22a) is even more reactive than in $(MeO)_3PO$ (99), giving the order of decreasing reactivity in the series $(MeO)_2P(O)Y$ (106): Y = NC_2H_4 (22a) > OMe (99) ≫ NMe_2 (21). The observed order of reactivity parallels the order of electron-releasing ability of the group Y as measured by the resonance substituent constants, σ_R^o, for the NC_2H_4, OMe and NMe_2 groups (-0.38, -0,45, and -0,52, respectively).[71] Although the values for the rate constants, k_{P-O}, in (22a), (99) and (21) do not correlate linearly with the corresponding σ_R^o(Y) constants, the relative rates obtained confirm the unusually small electron-releasing effect of the ethylenimine substituent with respect to the phosphoryl centre.

5.2.2 P-N BOND CLEAVAGE

No P-N bond cleavage was detected in the alkaline hydrolysis of $(MeO)_2P(O)NMe_2$ (21). In 1.68 *M* NaOD at 31 °C k_{P-O} for (21) was 4×10^{-7} ℓ mol^{-1} s^{-1}. If it is assumed that the contribution of parallel P-N bond cleavage to the overall rate of reaction was less than 2%,* the upper limit of k_{P-N} for (21) can be estimated as $\sim 8 \times 10^{-9}$ ℓ mol^{-1} s^{-1}. The difference in reactivity of the P-O and P-N bonds in (21) ($k_{P-O}/k_{P-N} > 50$) results from the difference in the leaving ability of the MeO^- and Me_2N^- groups in the product-determining step of the reaction, *i.e.*, collapse of the pentavalent intermediate formed by attack of the hydroxide ion at the phosphoryl centre.

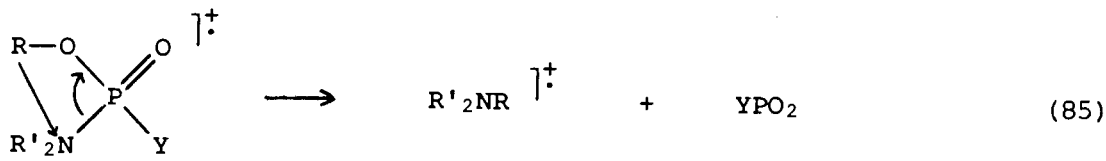
*Experiments carried out with mixtures of authentic samples showed that 2% dimethylamine would be detected by ^1H n.m.r. in the presence of (21) and its hydrolysis products.

This marked difference in reactivity of the P-O and P-N bonds observed in the hydrolysis of (21) was absent in (22a); in the latter compound P-N bond cleavage competed successfully with P-O bond fission (Eq. 84).



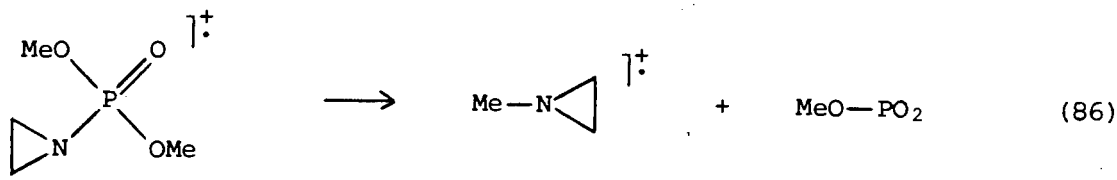
In 1.68 *M* NaOD solution at 31 °C cleavage of the amide bond in (22a) (k_{P-N} = 3.3 x 10^{-4} ℓ mol^{-1} s^{-1}) was somewhat faster than cleavage of the ester linkage (k_{P-O} = 2.9 x 10^{-4} ℓ mol^{-1} s^{-1}). As far as can be established this is the first known case of greater reactivity of the P-N bond relative to the P-O bond in nucleophilic displacement reactions of phosphoramidates taking place without prior activation of the P-N bond by acid catalysis.[36] In the alkaline hydrolysis of the cyclic amide (102) studied by Hudson *et. al.*[28] P-N bond cleavage contributed only 5% to the overall extent of the reaction. Since the upper limit of k_{P-N} for $(MeO)_2P(O)NMe_2$ (21) is estimated as 8 x 10^{-9} ℓ mol^{-1} s^{-1} the P-N bond in (22a) must have been hydrolysed faster than the P-N bond in (21) by a factor of at least 4 x 10^4. Thus the presence of the ethylenimine substituent in tertiary phosphoramidates has a profound effect on the reactivity of both the adjacent ester function and on the P-N bond itself. The difference in reactivity between (21) and (22a) is indicative of a large difference in the electron density at the nitrogen atoms of these substrates.

In the study of the electron impact-induced fragmentation behaviour of phosphoramidates discussed in Chapter 4, P-N bond cleavage accompanied by migration of an ester R group from oxygen to nitrogen was observed (Eq. 85).[72]



(85)

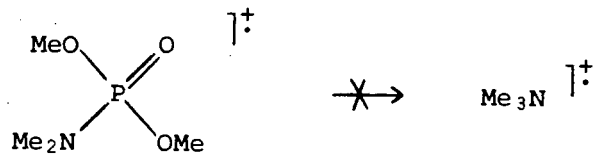
It was postulated that the ester R group migrates with its bonding electrons to the electron deficient nitrogen atom. In agreement with this, O → N methyl migration and formation of the N-methylethylenimine radical ion was observed in the mass spectrum of (22a) (see Eq. 86).



(86)

(22a)

No methyl group migration was observed in the spectrum of (21), *i.e.*, the trimethylamine radical ion was not formed (Eq. 87).



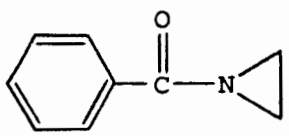
(87)

(21)

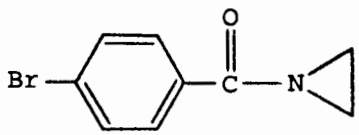
These results also indicate a difference in electron density between the nitrogen atoms of phosphoramidates (21) and (22a).

The large shift to higher wavenumber of the carbonyl stretching frequency in N-acetylethylenimine (97), $\nu_{C=O}$ = 1706 cm^{-1}, compared with the tertiary amide CH_3CONMe_2, $\nu_{C=O}$ = 1652 cm^{-1}, reflects reduced resonance interactions

between the carbonyl group and the nitrogen atom of the ethylenimine ring.[64] Further evidence for the absence of any significant interaction between the ethylenimine ring and an adjacent acyl group was obtained from an investigation of certain molecular parameters of N-benzoylethylenimine (109) and its *para*-brominated derivative (110).[73]

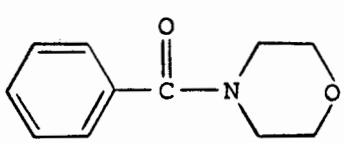


(109)



(110)

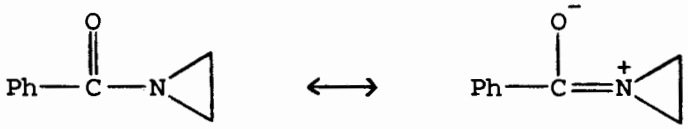
An investigation of the ^{13}C n.m.r. spectrum of (109) showed that the carbonyl carbon atom was deshielded by *ca.* 8 - 9 ppm compared with a series of N,N-disubstituted benzamides.[73] Evidence that structural effects were responsible for the unusually low-field carbonyl carbon resonance was obtained from the crystal structure determination of (110).[73] The unusual features of this structure were the pyramidal nitrogen atom and the C(O)—N bond length of 1.41 Å; by contrast the corresponding bond in N-benzoylmorpholine (111) was 1.34 Å with a planar nitrogen atom.[73]



(111)

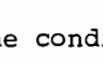
A variable temperature study of the ^{1}H n.m.r. spectrum of (109) showed that at temperatures as low as -155 °C (109) was still undergoing rapid exchange as only one signal was observed for the hydrogens of the ethylenimine ring. Such experimental evidence is consistent with a rapidly inverting pyramidal nitrogen atom.[73] The crystallographic and ^{1}H n.m.r. studies show that the C-N bond in (109) and (110) has substantially greater single bond character

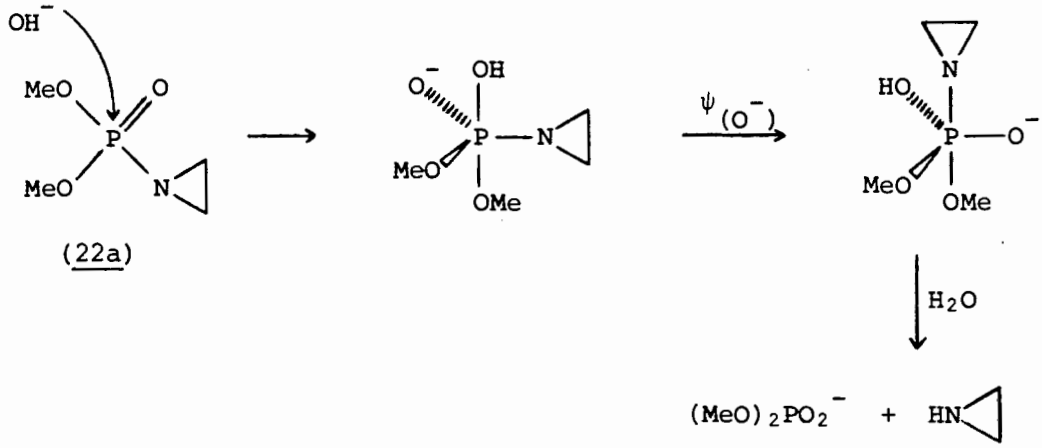
than the C-N bonds of other cyclic amides such as (111). The canonical form (109), shown below, thus appears to be the dominant contributor to the resonance hybrid for N-benzoylethylenimine (109) in solution.



(109)

Evidence for a rapidly-inverting pyramidal nitrogen atom in N-phosphorylated ethylenimines was obtained from the variable temperature ^1H n.m.r. study of $Ph_2P(O)N$  (22c).[74] A sharp doublet at room temperature (associated with spin-spin coupling of the hydrogens of the ethylenimine ring to the phosphorus nucleus) was observed in the n.m.r. spectrum of (22c). The doublet broadened only at very low temperature, -113 °C. This indicates that in phosphoramidates there is little conjugative interaction between the phosphoryl centre and the nitrogen atom of the ethylenimine ring. The crystal and molecular structure of (22c) was determined in this laboratory and is discussed in Chapter 6.

Under alkaline conditions $(MeO)_2P(O)N$  (22a) undergoes P-N bond cleavage while the P-N bond in $(MeO)_2P(O)NMe_2$ (21) is stable. The absence of any significant conjugative interaction between the nitrogen atom and the adjacent acyl or phosphoryl centre discussed above is the most likely reason for an increase in the rate of both steps of the nucleophilic substitution reaction, *viz.* attack of the nucleophile (OH^-) at the phosphorus atom [which also accelerates the rate of P-O bond cleavage relative to $(MeO)_3PO$ (99)] and collapse of the P^V intermediate, with ethylenimine being a good leaving group. The pK_a values of the conjugate acids of ethylenimine and dimethylamine are 8.01 and 10.73, respectively.[75] The mechanism proposed for P-N bond cleavage of (22a) in aqueous alkaline solution is shown in Eq. 88.

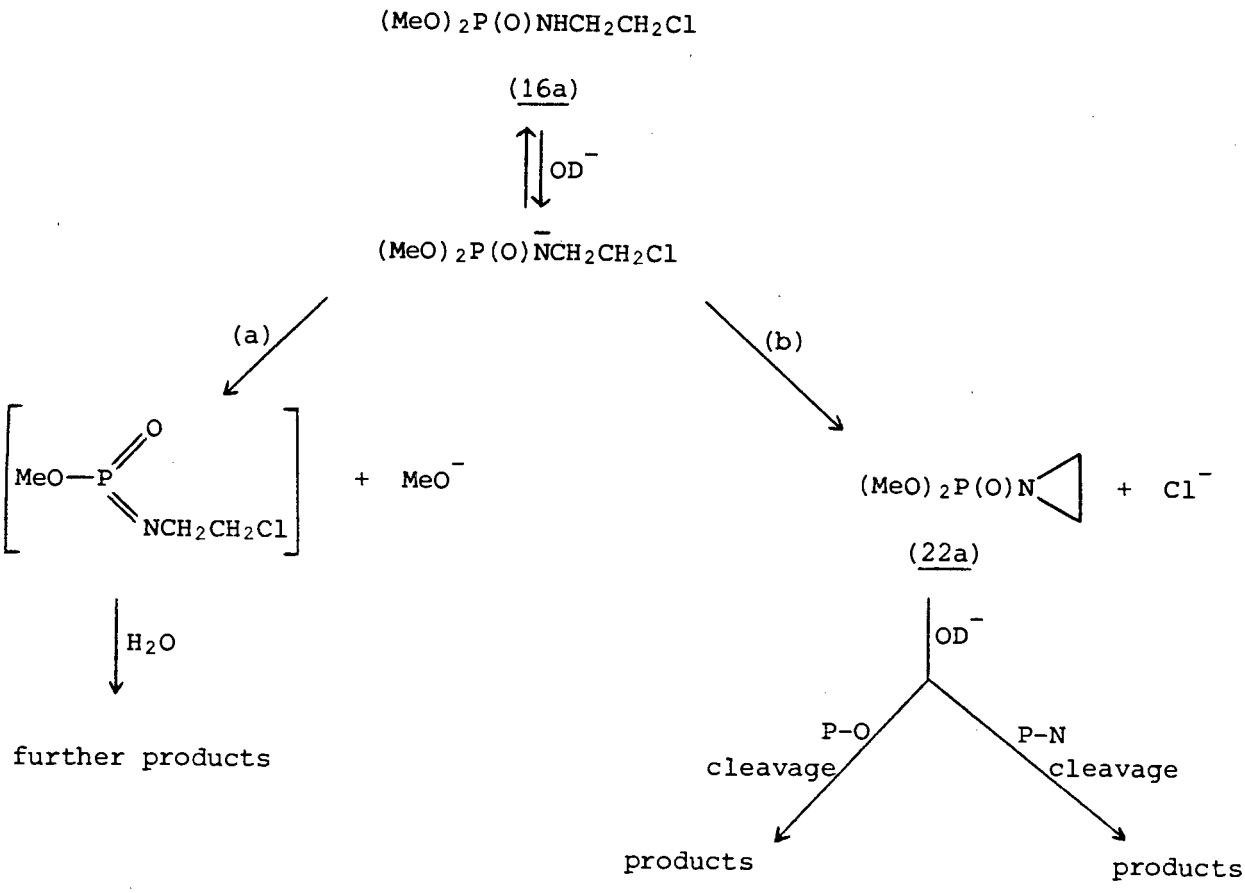


(22a) (88)

It was found that the ratio k_{P-O}/k_{P-N} for the hydrolysis of $(MeO)_2P(O)N$ (22a) depended to some extent on the sodium deuteroxide concentration. As $[OD^-]$ was varied from 0.84 *M* to 3.38 *M* k_{P-O}/k_{P-N} for the hydrolysis of (22a) changed from 0.59 to 1.21 (statistically corrected for the number of potential methoxide leaving groups). It therefore appears that base catalysis is less important for amide bond cleavage in (22a) than for ester bond cleavage, with the consequence that (22a) was hydrolysed very slowly in pure water ($t_{\frac{1}{2}}$ = 85 hours), and only *via* P-N bond cleavage. It should be noted that both $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_3PO$ (99) were indefinitely stable in water, within the accuracy of the ^1H n.m.r. measurements. The observed variation in the regioselectivity in the hydrolysis of (22a) may imply that the product-determining step, *i.e.*, departure of the ethylenimine group [Eq. 84 pathway (b)], has a greater requirement for electrophilic assistance by water than does cleavage of the P-O bond. On the other hand, the variations in the ratio k_{P-O}/k_{P-N} are rather small considering the range of sodium deuteroxide concentration used and may result from some changes in general solvation properties of the reaction medium affecting the two product-determining steps (Eq. 84) in different ways.

5.2.3 HYDROLYSIS OF $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a)

There are, in principle, two pathways available for the hydrolysis of (16a) as shown in Scheme 14.

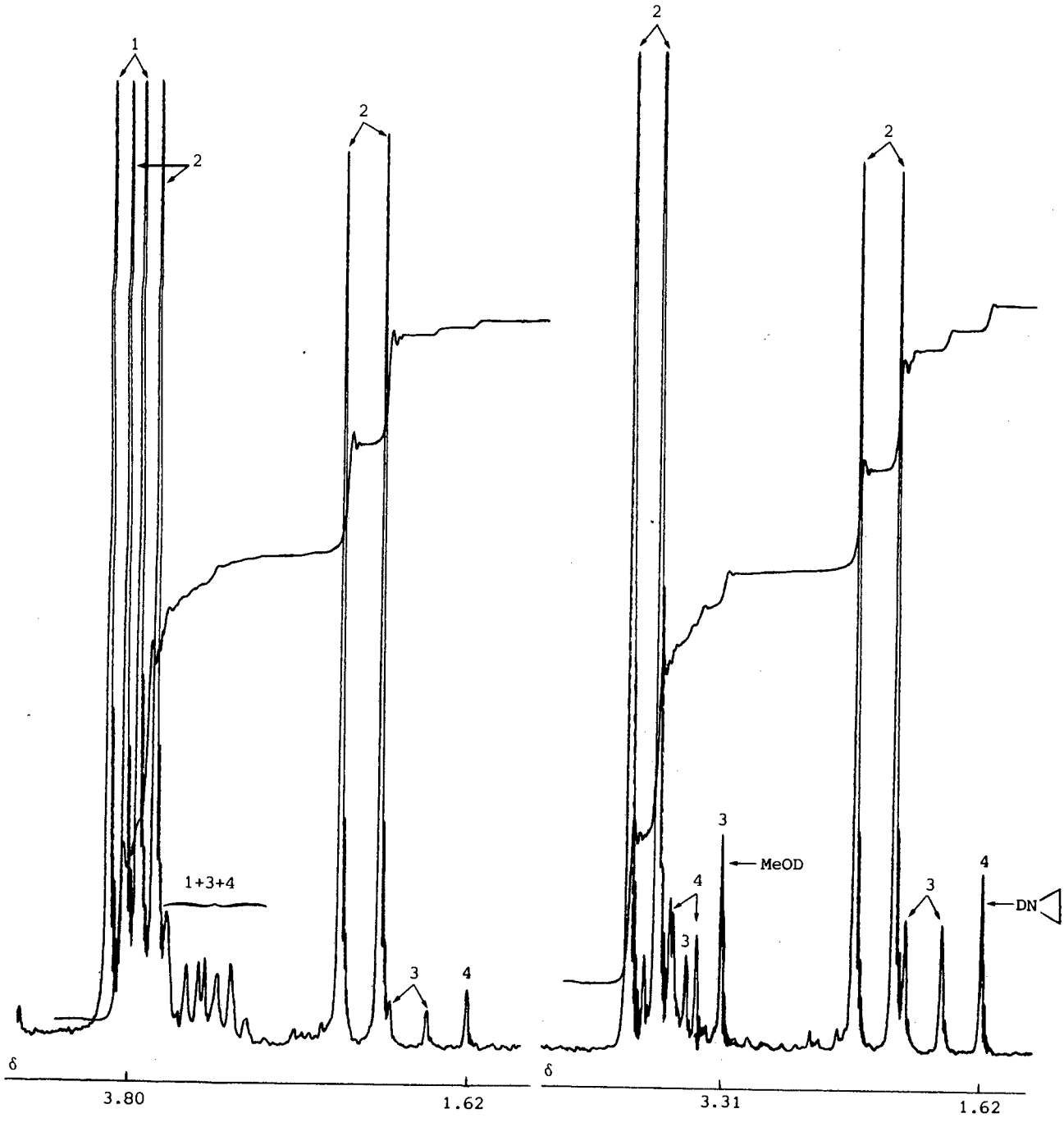


Scheme 14

Pathway (a), which is analogous to Eq. 83, would result in P-O bond cleavage only, while pathway (b) yielding (22a) would be followed by hydrolysis of this compound as shown in Eq. 84. When (16a) was dissolved in aqueous sodium deuteroxide, the ^1H n.m.r. spectrum (Figure 15) showed rapid formation of (22a) followed by the formation of methanol and ethylenimine with rates very close to those obtained for the hydrolysis of (22a).

It was difficult to measure accurately the rates of P-O and P-N bond cleavage in $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) since initial ring closure to form

Figure 15 $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) (0.32 *M*), in NaOD (2.16 *M*) showing rapid formation of $(MeO)_2P(O)N$  (22a) and its hydrolysis products



Spectrum recorded 4 mins 50 sec after mixing

Spectrum recorded 7 mins 15 sec after mixing

1 $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) 2 $(MeO)_2P(O)N$  (22a)

3 $(MeO)(NC_2H_4)PO_2^-$ + MeOD; products of P-O bond cleavage

4 $(MeO)_2PO_2^-$ + DN  ; products of P-N bond cleavage

$(MeO)_2P(O)N\triangleleft$ (22a) resulted in a reaction mixture which had a fairly complex ^1H n.m.r. spectrum (see Figure 15). It was, however, possible to measure the ratio k_{P-O}/k_{P-N} from the cleavage products as shown in Figure 16.

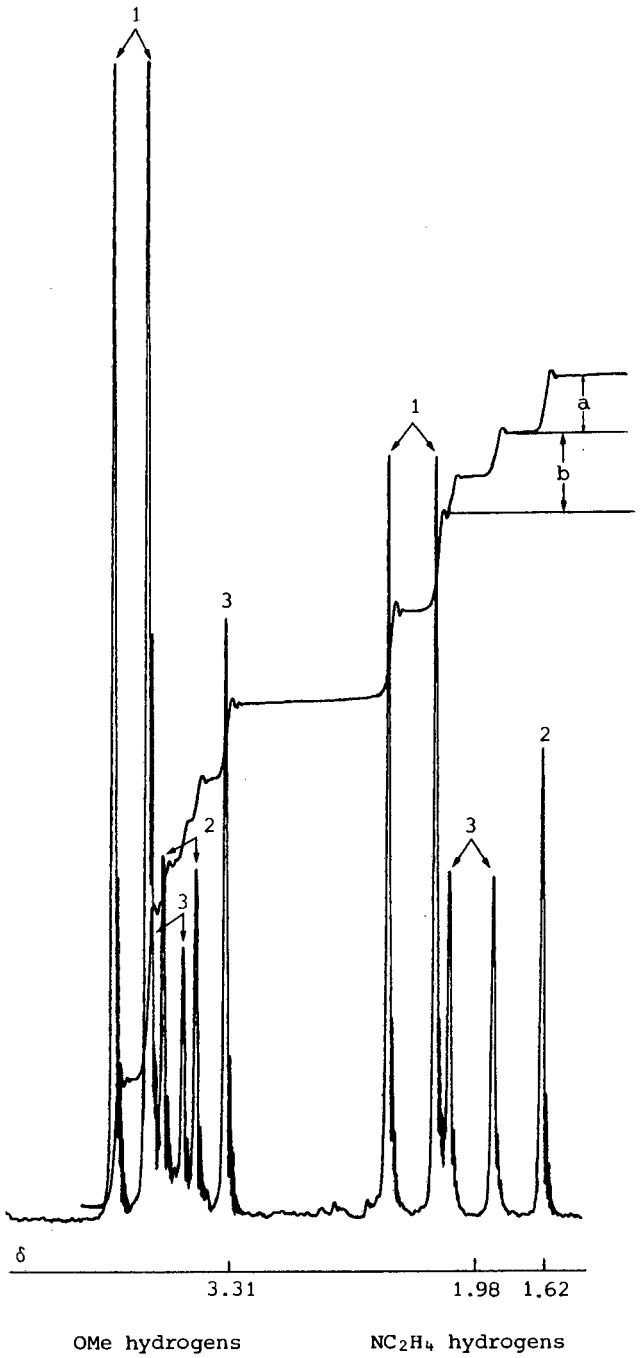
It should be noted that for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) any contribution by pathway (a) (Scheme 14) would increase the proportion of methanol relative to ethylenimine. This ratio was, however, constant throughout each kinetic run indicating a single pathway for the hydrolysis reaction. The dependence of k_{P-O}/k_{P-N} for (16a) on hydroxide ion concentration was similar to that measured for (22a). The ratio k_{P-O}/k_{P-N} for (16a) and (22a) at varying hydroxide ion concentrations is presented in Table 15 and illustrated in Figure 17.

Table 15 Variation of k_{P-O}/k_{P-N} with $[OD^-]$ for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) and $(MeO)_2P(O)N\triangleleft$ (22a)

	$[OD^-]$	k_{P-O}/k_{P-N}
(16a) 0.319 *M*	0.838	0.63
	2.160	0.73
	3.380	1.04
	6.750	1.60
(22a) 0.331 *M*	0.838	0.59
	1.677	0.85
	3.377	1.21

The fact that the variation of k_{P-O}/k_{P-N} with OD^- concentration is virtually the same for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) and $(MeO)_2P(O)N\triangleleft$ (22a) shows that in aqueous alkaline solutions (16a) behaved simply as a precursor of (22a) which then reacted as shown in Eq. 84. This result shows that the nucleophilic nitrogen atom of the conjugate base of (16a) preferentially attacked

Figure 16 Determination of the ratio k_{P-O}/k_{P-N} for the hydrolysis of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a), which proceeds *via* rapid initial formation of $(MeO)_2P(O)N\triangleleft$ (22a)



1 $(MeO)_2P(O)N\triangleleft$ (22a)

2 $(MeO)_2PO_2^-$ + $DN\triangleleft$; products of P-N bond cleavage

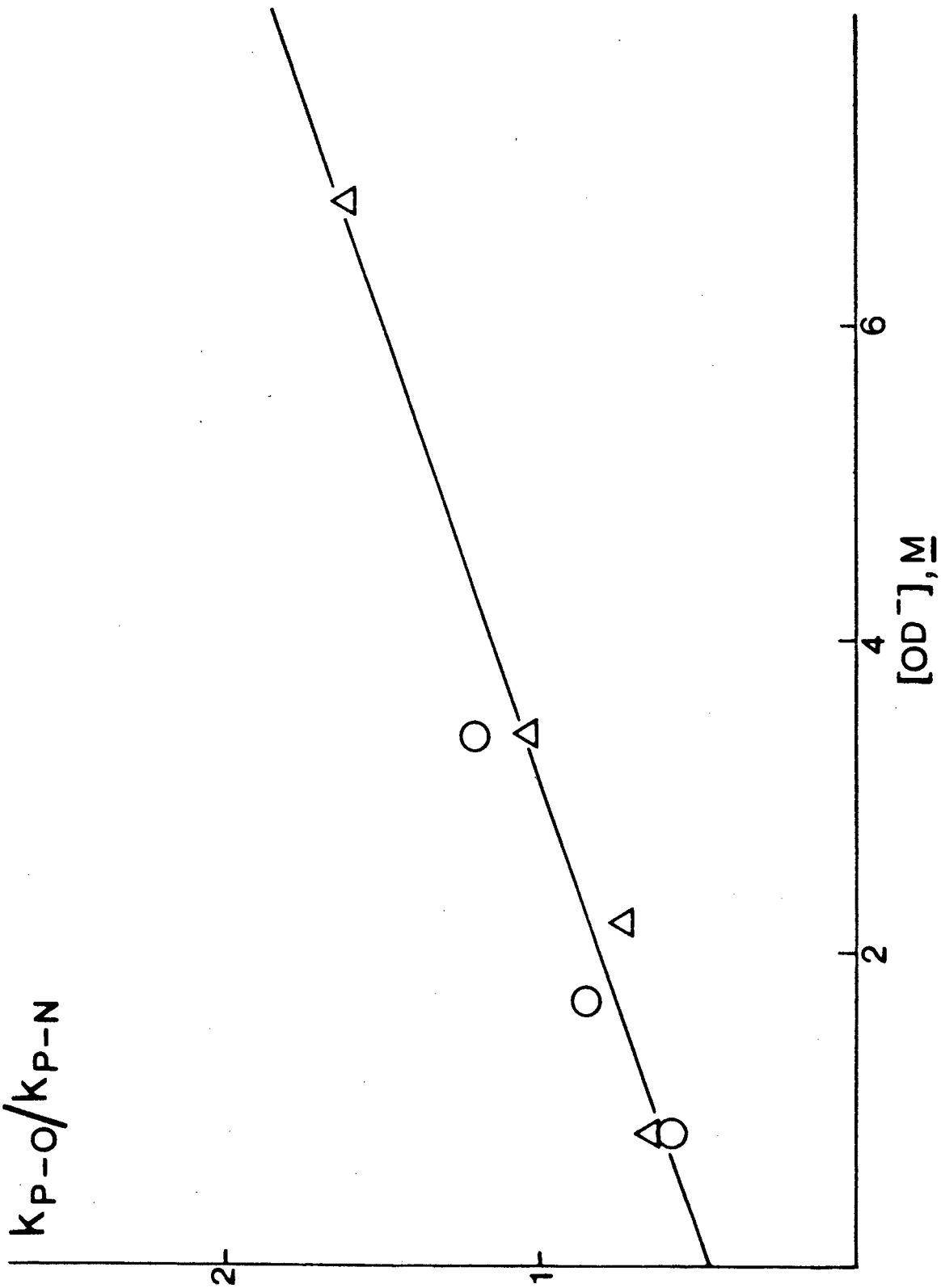
3 $(MeO)(NC_2H_4)PO_2^-$ + MeOD; products of P-O bond cleavage

k_{P-O} is measured by the integrated height of the doublet at δ 1.98 statistically corrected for the number of potential methoxide leaving groups

k_{P-N} is measured by the integrated height of the singlet at δ 1.62

i.e. $k_{P-O}/k_{P-N} = \frac{(b \div 2)\ mm}{a\ mm}$

Figure 17 Variation of k_{P-O}/k_{P-N} with OD^- concentration for the hydrolysis of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) (triangles) and $(MeO)_2P(O)N$ (22a) (circles).



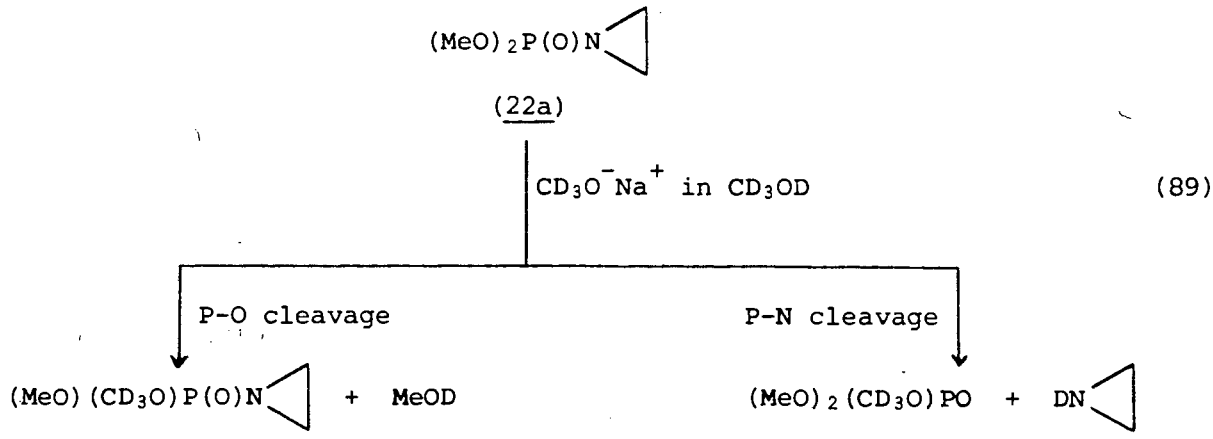
the β-carbon atom to give (22a) and Cl^- [Scheme 14 pathway (b)] rather than donating its electrons to the phosphorus atom to release methoxide ion and a metaphosphate species [Scheme 14 pathway (a)].

It should be noted that in an attempt to prepare $(PhO)_2P(O)N$◁ (22d) by reaction of $(PhO)_2P(O)NHCH_2CH_2Cl$ (16b) with sodium hydride (see Chapter 3.2.1), a large quantity of phenol was formed and the required product was not obtained. This result indicates that if a better leaving group such as phenoxide is present at the phosphorus atom the conjugate base of the secondary phosphoramidate is capable of expelling that group.

5.2.4 REACTIONS WITH OTHER NUCLEOPHILES

METHOXIDE ION AS A NUCLEOPHILE

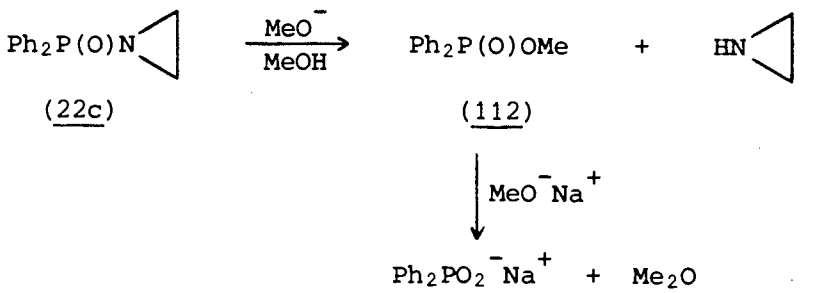
The obvious difference between the reactivity of the two tertiary phosphoramidates $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_2P(O)N$◁ (22a) was also confirmed with respect to the methoxide ion. At 25 °C (21) remained unchanged for 44 hours in a methanolic solution containing an equimilar quantity of sodium methoxide while under the same conditions (22a) reacted *via* both P-O and P-N bond cleavage (Eq. 89).



(89)

After 24 hours a 20% conversion to products was obtained and the ratio of MeOD to DN formed (a measure of k_{P-O}/k_{P-N}) was 2.2 which is not significantly different from the analogous ratios (0.6 - 1.2) observed in aqueous hydroxide media. These results indicate that the low P-O/P-N regioselectivity in the nucleophilic cleavage of $(MeO)_2P(O)N$  (22a) is of a general nature.

Similarly $Ph_2P(O)N$  (22c) reacted easily with methoxide ion to give ethylenimine and methyl diphenylphosphinate (112) which then underwent demethylation to give sodium diphenylphosphinate (Eq. 90).

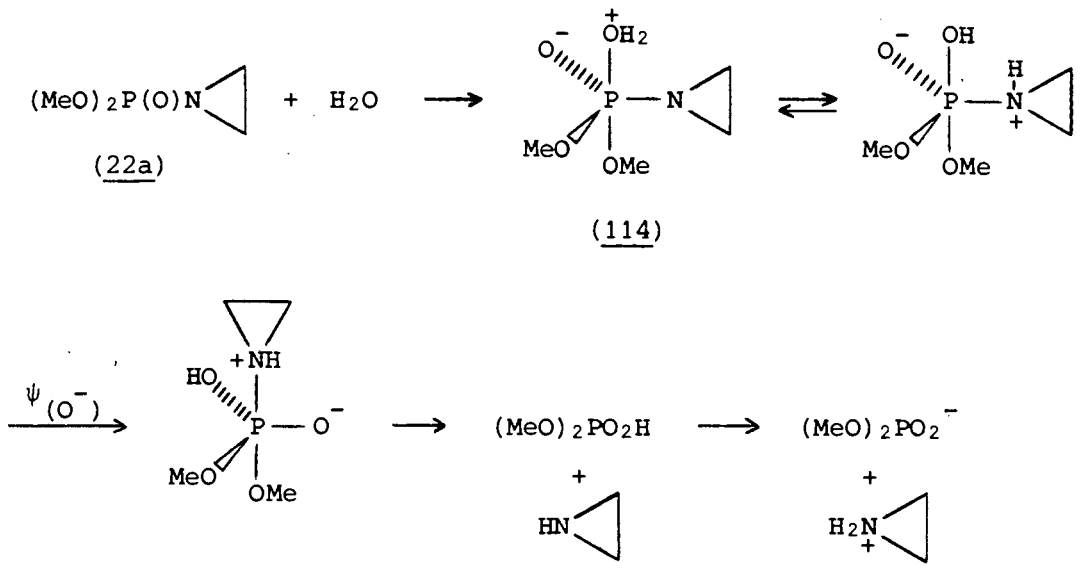


(90)

At 25 °C the cleavage of the P-N bond in (22c) was complete within 70 hours. The observed behaviour of (22c) contrasts with the low reactivity reported by Haake[8] for its N,N-dimethyl analogue, $Ph_2P(O)NMe_2$ (113), towards nucleophilic cleavage of the P-N bond. At 90 °C $t_{\frac{1}{2}}$ for (113) in NaOH was 34 hours.

WATER AS A NUCLEOPHILE

As mentioned in Chapter 5.2.2, the phosphoramidate $(MeO)_2P(O)N$  (22a) solvolysed slowly in pure water with exclusive P-N bond cleavage ($k = 2.3 \times 10^{-6}$ s^{-1} at 31 °C) while $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_3PO$ (99) remained unchanged in this medium. The proposed mechanism for this reaction is shown in Eq. 91.



(22a) (114)

(91)

We believe that the nitrogen atom in the pentavalent intermediate (114) is more basic than any of the oxygen atoms. Thus the equilibrium constant, K, for proton transfer to nitrogen is greater than for any of the oxygen atoms giving the leaving group, HN  .

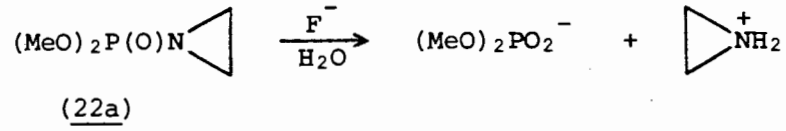
FLUORIDE ION AS A NUCLEOPHILE

The fluoride ion (which is known to catalyse nucleophilic displacement at phosphorus)[70] accelerated the hydrolysis in water of both $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_2P(O)N$  (22a); the reactivity of (22a) was again much greater than (21). (21) was incubated at 31 °C in water containing an equimolar quantity of NaF. After 7 days 8% dimethylammonium ion was formed (Eq. 92).

$$(MeO)_2P(O)NMe_2 \xrightarrow[H_2O]{F^-} (MeO)_2PO_2^- + Me_2\overset{+}{N}H_2 \qquad (92)$$

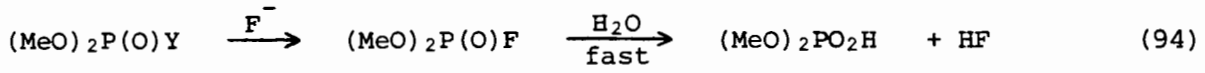
(21)

Under the same conditions P-N bond cleavage in (22a) was complete within 41 hours (Eq. 93).



(22a) (93)

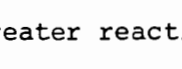
In the presence of an equimolar amount of $NaNO_3$ the half-life for the hydrolysis of (22a) in water was 85 hours, which was identical to that in pure water. The ionic strength of the solutions containing $NaNO_3$ and NaF was the same. Thus fluoride ion acceleration of hydrolysis is not due to the general salt effect but to the participation of F^- in the hydrolysis, probably as shown in Eq. 94.



(94)

(21) R = NMe_2

(22a) R = NC_2H_4

In conclusion, the presence of the ethylenimine subsitituent in the phosphoramidate (22a) has a profound effect on the rate of nucleophilic substitution, P-O bond cleavage is activated relative to the ester $(MeO)_3PO$ (99) while P-N bond cleavage occurs at a rate comparable to that of ester cleavage. The greater reactivity of  (22a) can be ascribed to the difference in the strength of the P-N bond in (22a) relative to $(MeO)_2P(O)NMe_2$ (21). The absence of any significant conjugative interation between the P=O group and the nitrogen atom in (22a) allows for both facile attack by nucleophiles at the phosphoryl centre as well as departure of the ethylenimine group from pentavalent intermediates such as (114) (Eq. 91).

CHAPTER SIX

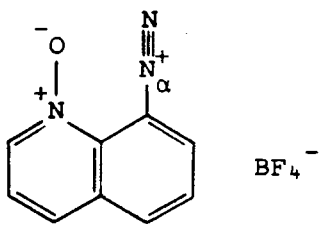
CRYSTAL AND MOLECULAR STRUCTURE

OF SELECTED PHOSPHINAMIDATES

6.1 INTRODUCTION

Although the N-(β-chloroethyl)phosphoramidates (15) and (16) have more than one nucleophilic centre (see Chapter 3.1 Schemes 2 and 3) intramolecular nucleophilic displacement occurred only *via* 1,3-attack by the amidate nitrogen atom at the β-carbon atom. The facile formation of the N-phosphorylated ethylenimines (22) and (50) from the phosphoramidates (16) and (15), respectively, was discussed in Chapter 3. The rapid cyclisation of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) to $(MeO)_2P(O)N$ (22a) in aqueous alkaline media was discussed in Chapter 5. It was thus of interest to detect an "early stage" of this ring closure reaction in the solid state using the approach outlined by Bürgi and Dunitz.[76]

Crystallography can provide important information about dynamic aspects of molecular structure. There are two ways of progressing from the static to the dynamic interpretation of results from crystal structures. The first is to exploit detailed information from one or more accurately determined structures. For example, Wallis and Dunitz[77] have determined the crystal structure of quinoline-8-diazonium-1-oxide tetrafluoroborate (115) at 95 K.



(115)

They found the oxygen atom at a distance of 2.44 Å from the α-nitrogen atom of the diazonium group, a distance which is well within the sum of the van der Waals radii (3.10 Å).[78] The inclination of the diazonium group towards the oxygen atom strongly suggests that the $O\cdots N_\alpha$ interaction is attractive.

The authors regard this crystal structure as an example of incipient nucleophilic attack on a diazonium group. The second method of using crystal structure data correlates relevant structural parameters from many compounds. The basic assumption behind this structural correlation method is that a distribution of sample points corresponding to observed structures would tend to be concentrated in low-lying regions of the potential energy surface.[76] This approach has been used in a study of the quaternary phosphonium salts $R_4P^+X^-$.[79] Exclusive "face" orientation of X^- with respect to the tetrahedral phosphonium centre was demonstrated, and analysis of the secondary interactions of X^- with the organic cation indicated that the systems studied were better models for ylid formation (α-hydrogen abstraction) than nucleophilic attack at the P^{IV} atom.[79]

In this work an approach similar to that used by Wallis and Dunitz[77] for (115) *viz.*, determination of a single crystal structure, was applied to $Ph_2P(O)NHCH_2CH_2Cl$ (16d), the precursor of $Ph_2P(O)N$◁ (22c), to detect any incipient interaction between the amidate nitrogen atom and the β-carbon atom. (16d) was chosen as the model for the N-(β-chloroethyl)phosphoramidates since single crystals suitable for X-ray analysis could be obtained. The phosphoramidates (15a,b), and (16a) on the other hand were liquids, and (16b) was a waxy solid.

The substantial difference in reactivity of the P-N bond of the tertiary phosphoramidates $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_2P(O)N$◁ (22a) towards nucleophiles was discussed in Chapter 5. These phosphoramidates are liquids. Thus the structure of the crystalline $Ph_2P(O)N$◁ (22c) was determined in these laboratories and compared with the previously reported[80] crystal structure of $Ph_2P(O)NMe_2$ (113). Attention was focussed on possible differences in the P-N bond lengths and on the pyramidality of the nitrogen atoms in (22c) and (113), parameters which might reflect the differences in chemical behaviour of (22c) and (113), and by analogy, to (21) and (22a).

6.2 RESULTS AND DISCUSSION

6.2.1 CRYSTAL AND MOLECULAR STRUCTURE OF $Ph_2P(O)NHCH_2CH_2Cl$ (16d)

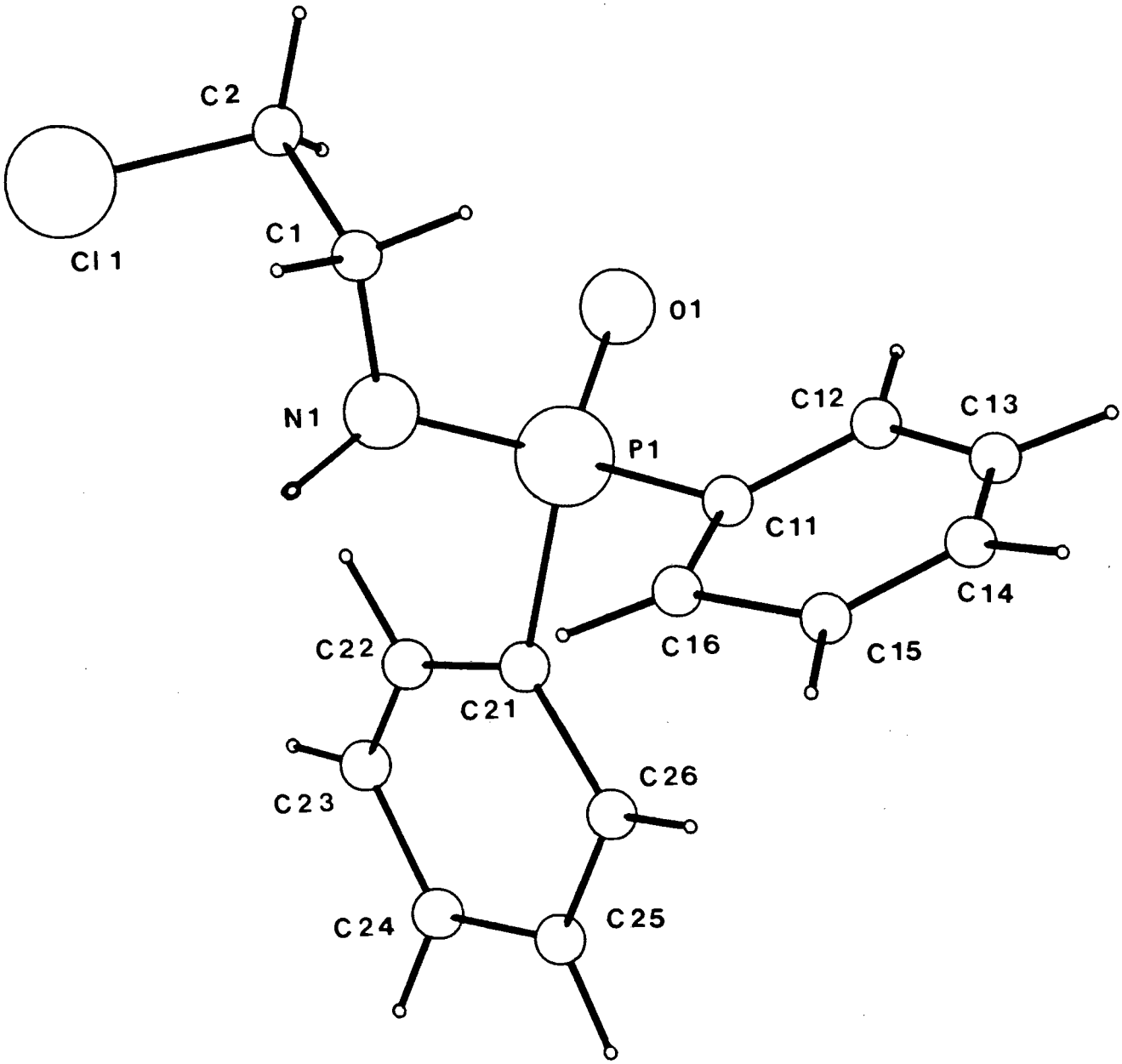
The molecular parameters obtained in this work are listed in Table 16. (16d) had 4 crystallographically independent molecules per unit cell, *viz.*, A, B, C, D.

Table 16 Selected molecular parameters for $Ph_2P(O)NHCH_2CH_2Cl$ (16d)

		A	B	C	D
Bond lengths, Å	P-O	1.51(1)	1.42(2)	1.46(2)	1.53(2)
	P-N	1.65(2)	1.64(2)	1.60(2)	1.60(2)
	P-C11	1.90(1)	1.77(1)	1.70(1)	1.79(1)
	P-C21	1.91(2)	1.82(2)	1.68(1)	1.75(2)
	N-C	1.46(2)	1.42(2)	1.46(2)	1.51(2)
Bond angles, deg	N1-P1-01	108(1)	118(1)	119(1)	108(1)
	C11-P1-01	109(1)	111(1)	109(1)	119(1)
	C11-P1-N1	112(1)	106(1)	107(1)	100(1)
	C21-P1-01	122(1)	112(1)	106(1)	107(1)
	C21-P1-N1	102(1)	105(1)	104(1)	115(1)
	C21-P1-C11	104(1)	104(1)	111(1)	108(1)
	H1-N1-P1	121(1)	124(1)	121(1)	128(1)
	C1-N1-P1	120(1)	126(1)	121(1)	117(1)
	C1-N1-H1	109(1)	109(1)	114(1)	108(1)
Torsion angle, deg	N-C1-C2-Cl	81(1)	75(2)	-67(1)	-14(6)
Non-bonded distance, Å	O···C2	3.33(2)	3.43(2)	3.62(2)	3.67(2)
Deviation of N1 from H C P plane, Å		0.23(2)	0.10(2)	0.17(2)	0.21(2)
Non-bonded distances, Å		O1A···N1D	2.78(2)	O1B···N1C	2.71(2)
		O1C···N1B	2.76(2)	O1D···N1A	2.85(2)

A perspective view of $Ph_2P(O)NHCH_2CH_2Cl$ (16d) is shown in Figure 18 and a packing diagram is shown in Figure 19.

Figure 18 A perspective view of $Ph_2P(O)NHCH_2CH_2Cl$ (16d)



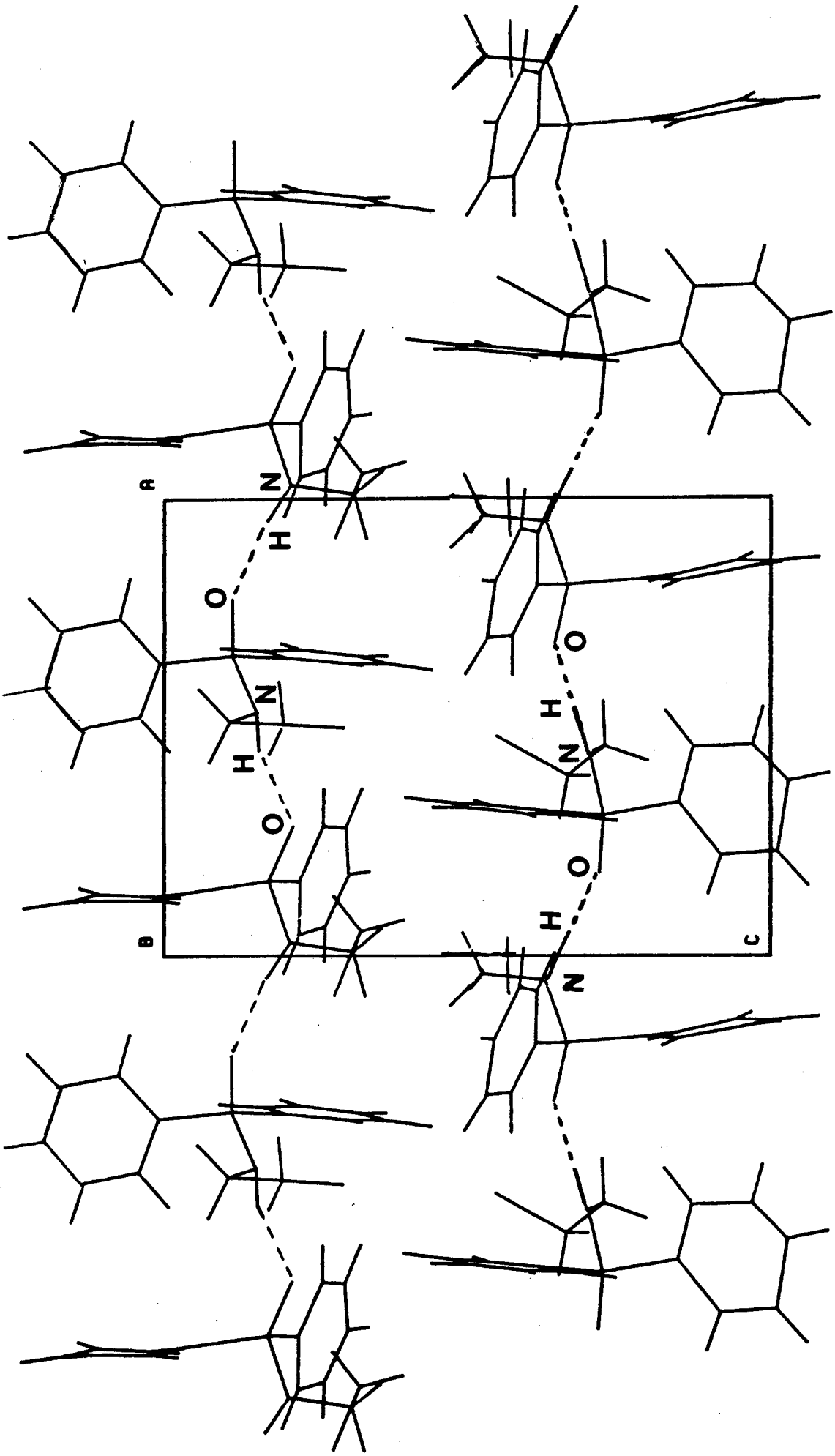
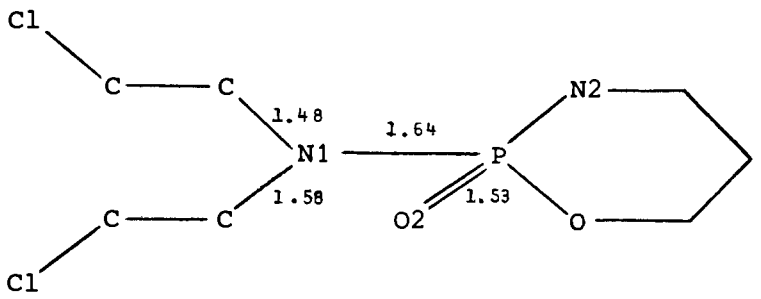


Figure 19 Packing diagram of $Ph_2P(O)NHCH_2CH_2Cl$ (16d); hydrogen bonding is indicated by dotted lines.

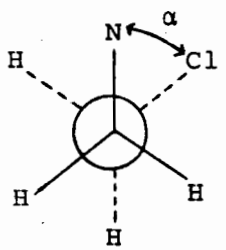
The P-O, P-N and N-C bond lengths for $Ph_2P(O)NHCH_2CH_2Cl$ (16d) are similar to those reported for (+)-cyclophosphamide (4)[81] (see Figure 20) and the phosphoric anilides $(MeO)_2P(O)NHAr$.[82]

Figure 20 Relevant bond lengths (Å) for (+)-cyclophosphamide (4). Standard deviations of the bond lengths are 0.02 - 0.03 Å



The angles at the phosphorus atom, in the range 100 - 122° indicate that the configuration is largely tetrahedral. A similar variation in these angles was reported for (+)-cyclophosphamide (4).[81] The angles at the nitrogen atom, in the range 108 - 128°, indicate that it is more tetrahedral than the nitrogen atom N1 of (4).[81] The deviation of the nitrogen atom from the H C P plane for the four molecules of (16d) is in the range 0.10 - 0.23 Å, which is of the same order as the value of 0.2 Å calculated for (4) using data from Reference 81. The non-bonded distance O1···C2, *i.e.*, O···C_β, for (16d), molecule A, is 3.33 Å which is slightly greater than the sum of the van der Waals radii (3.20 Å).[78] The O1···C2 non-bond distance for molecules B, C and D are all greater than 3.4 Å; hence even for molecule A there is no obvious interaction between the phosphoryl oxygen and the β-carbon atom in the crystal.

The torsion angle N-C1-C2-Cl in (16d) varies from -67 to 81°.* No explanation for the large variation in the values observed is available at present. Thus the nitrogen and chlorine atoms are clearly not antiperiplanar, which would be the most favourable conformation for nucleophilic displacement of the chloride ion by the amidate nitrogen atom. Studies of acyclic systems (where rotation about the carbon-carbon bond yields any potentially available torsion angle) show that a torsion angle of 180° (antiperiplanar) leads to more facile elimination than any other angle.[84] The Newman projection formula for (16d) drawn along the C1-C2 bond shows, however, that the nitrogen and chlorine atoms are in the unfavourable gauche or nearly eclipsed conformations:



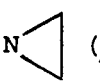
$|\alpha| = 14 - 81°$

Intermolecular hydrogen bonding occurs in (16d) yielding *trans*-polymeric chains as shown in Figure 19. This contrasts with the hydrogen bonding in the phosphoramidates $(MeO)_2P(O)NHAr$ in which the conformation of the >P(O)NH< moiety was *cis* yielding dimers or *cis* polymeric chains.[82] It is proposed that the stability arising from the intermolecular hydrogen bonding in $Ph_2P(O)NHCH_2CH_2Cl$ (16d) is a predominant factor in determining the packing of the molecules in the crystal lattice. This has occurred at the expense of a

*The torsion angle $\omega(I\text{-}J\text{-}K\text{-}L)$ is defined as the angle between the vector $J\text{-}I$ and the vector $K\text{-}L$ when viewed down $J\text{-}K$. The sign of ω is positive if $J\text{-}I$ is to be rotated clockwise into $K\text{-}L$ and negative if counter-clockwise.[83]

favourable torsion angle close to 180° for the N-(β-chloroethyl) group. In (+)-cyclophosphamide (4) the torsion angle N1-C1-C2-Cl varied over the range 176 - 180°. Hydrogen bonds are formed between the phosphoryl group and HN of three (+)-cyclophosphamide molecules which are related by a three-fold axis in the unit cell, and trimers are formed. The O2···N2 distance in (4) is 2.84 Å[81] compared to 2.71 - 2.85 Å in $Ph_2P(O)NHCH_2CH_2Cl$ (16d).

In conclusion, it can be seen that for $Ph_2P(O)NHCH_2CH_2Cl$ (16d) there is no correlation between the crystal structure and its behaviour in solution. Treatment of (16d) with Ag^+/OH^- or NaH led to facile formation of $Ph_2P(O)N$ (22c). In the solid state the four molecules of (16d) adopt gauche or nearly eclipsed conformations about the α- and β-carbon atoms of the N-(β-chloroethyl) groups and the torsion angle for N1-C1-C2-Cl varies from -67 to 81°. The most favourable conformation for the reaction observed in solution, *viz.*, attack by the amidate nitrogen atom, would require a torsion angle of 180°. It is believed that the unfavourable conformations of the N-(β-chloroethyl) groups in the solid state are a result of the intermolecular hydrogen bonding.

6.2.2 CRYSTAL AND MOLECULAR STRUCTURE OF $Ph_2P(O)N$  (22c); A COMPARISON WITH THE STRUCTURE OF $Ph_2P(O)NMe_2$ (113)

The molecular parameters obtained in this work for (22c) are listed in Table 17 together with those reported for (113).[80]

Table 17 Selected molecular parameters for $Ph_2P(O)N$⟨ (22c) and $Ph_2P(O)NMe_2$ (113)

		$Ph_2P(O)N$⟨ (22c)	$Ph_2P(O)NMe_2$ (113)[1]
Bond lengths, A	P-O	1.479(3)	1.482(5)
	P-N	1.672(3)	1.681(6)
	P-C11	1.799(4)	1.794(8)
	P-C21	1.792(3)	1.784(8)
	N-C	1.472(5)	1.50
		1.465(4)	1.48
	C1-C2	1.464(5)	-
Bond angles, deg	C1-N1-P1	117.9(2)	118.0(5)
	C2-N1-P1	118.2(2)	115.8(6)
	C1-N1-C2	59.8(2)	115.1(7)
Deviation of nitrogen from C1 P C2 plane, *d*		0.690	0.303

1 Data taken from Ref. 80.

A perspective view of $Ph_2P(O)N$⟨ (22c) is shown in Figure 21. The P-O bond lengths in $Ph_2P(O)N$⟨ (22c) and $Ph_2P(O)NMe_2$ (113) are similar to those quoted for (+)-cyclophosphamide (4),[81] $(MeO)_2P(O)NHAr$[82] and $Ph_2P(O)NHCH_2CH_2Cl$ (16d) (Table 16). The P-N bond lengths in (22c) and (113) are identical (within experimental error) and are similar to those reported for (4),[81] $(MeO)_2P(O)NHAr$[82] and (16d). An important difference between the molecular parameters of (22c) and (113) is the pyramidality of the amidate nitrogen atom, *i.e.*, the deviation *d* of the nitrogen atom from the C P C plane, which can be taken as an indication of the difference in hybridisation and may be related to the chemical behaviour of these compounds.

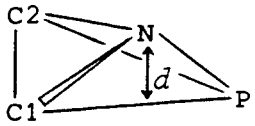
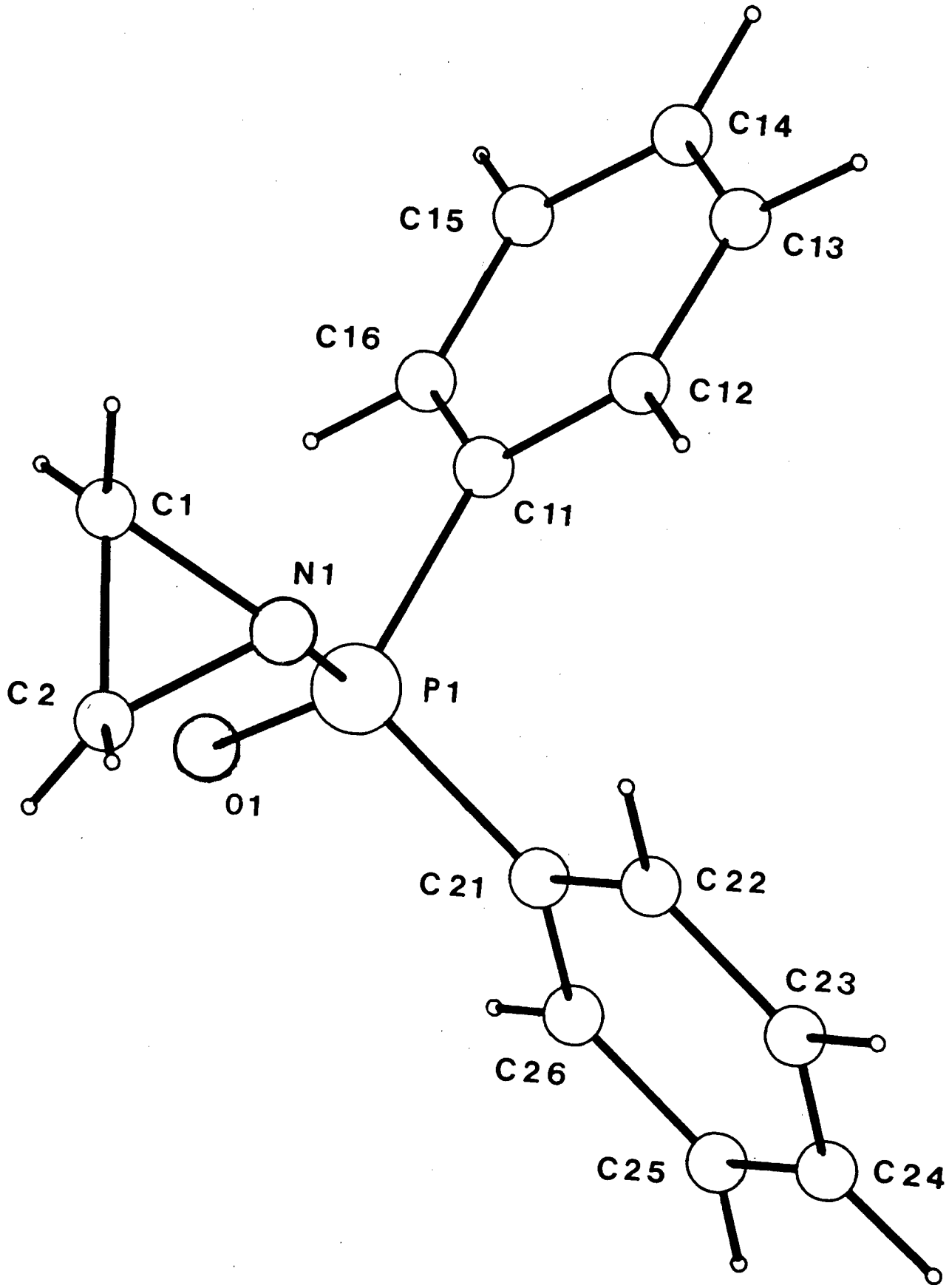
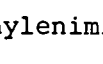


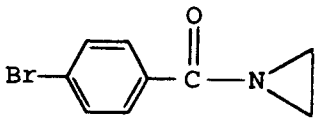
Figure 21 A perspective view of $Ph_2P(O)N$ (22c)



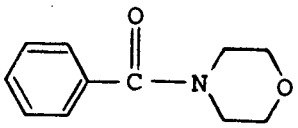
The angles at the nitrogen atoms of (22c) and (113) are also different due to the three-membered ring in (22c) (See Table 17).

The N-phosphorylated ethylenimines such as $(MeO)_2P(O)N$  (22a) are much more reactive towards nucleophiles than the corresponding N,N-dimethylamino derivative $(MeO)_2P(O)NMe_2$ (21) (see Chapter 5.2). This difference in reactivity was ascribed to the lack of conjugative interaction between the nitrogen atom and the adjacent phosphoryl centre in (22a), which allows facile attack by nucleophiles. The N,N-dimethylamino group in (21) deactivates this compound towards nucleophilic substitution by donating its electrons to the phosphoryl centre.[68] The observed chemical behaviour of (21) and (22a) is reflected in the crystal structures of their phosphinamidate analogues $Ph_2P(O)NMe_2$ (113) and $Ph_2P(O)N$  (22c). The nitrogen atom in (113) is much more planar than that of (22c) (see Table 17), which shows a greater possibility for $d_\pi - p_\pi$ overlap between the phosphorus and nitrogen atoms in (113) relative to (22c), and by analogy, in (21) and (22a).

It is interesting to note, however, that the decrease in reactivity of (113) relative to (22c) is not reflected by a decrease in the length of the P-N bond with a concomitant increase of the length of the P-O bond (see Table 17). This contrasts with the analogous molecular parameters measured for carboxamides: studies of N-acylated ethylenimines and their N,N-disubstituted analogues showed that conjugative interactions in the latter compounds led to a decrease in the C(O)-N bond length and an increase in the C-O bond length. Thus the C-N bond length in N-(4-bromobenzoyl)ethylenimine (110) is 1.41 Å while that in N-benzoylmorpholine (111) is 1.34 Å.[73] The nitrogen atom in (110) is pyramidal while in (111) it is planar.[73]



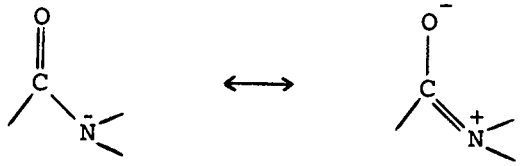
(110)

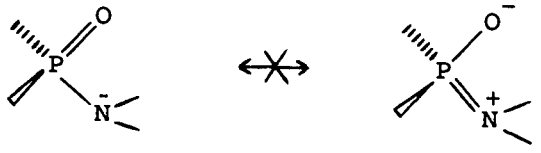


(111)

The increase in the length of the C-O bond in N,N-disubstituted carboxamides relative to N-acylated ethylenimines is reflected by the carbonyl stretching frequencies in CH_3CON△ and CH_3CONMe_2 which are 1706 and 1652 cm^{-1}, respectively.[64]

The X-ray crystal structures of the diphenylphosphinamidates (22c) and (113) show that there is little parallel between the resonance systems which can be written for carboxylic amides and phosphoramidates:





In conclusion, a comparison of selected molecular parameters of $Ph_2P(O)N$△ (22c) and $Ph_2P(O)NMe_2$ (113) shows that the difference in their reactivity in solution is reflected in the degree of pyramidality of the nitrogen atom as well as the ring-strain in (22c) (see bond angles about the nitrogen atom in Table 17). The shortening of the C-N bond and the increase in the length of the C-O bond due to conjugative interactions in carboxylic amides is not observed for the corresponding P-O and P-N bonds in phosphinamidates. The difference in pyramidality of the nitrogen atoms in (22c) and (113) implies

a difference in the hybridisation of the nitrogen atoms and this can be correlated with the difference in their chemical behaviour in solution. The difference in pyramidality of the nitrogen atom in phosphinamidates is, however, not reflected in the P-N bond length. These bond lengths are the same for both compounds, implying that the degree of $p_\pi - d_\pi$ bonding in (22c) and (113) is not significantly different. The results of kinetic experiments (see Chapter 5) show that electronically the N,N-dimethylamino and N-ethylene groups must be very different. The crystal structure results indicate that in the diphenylphosphinic derivatives the extent of $p_\pi - d_\pi$ N-P back-donation is not very important and that the ethylenimine moiety as a whole is less electron-donating than the N,N-dimethylamino group. In the Walsh model of cyclopropane each carbon atom is sp^2 hybridised.[85] This cyclic compound has an unusual "π-system" formed from the p-orbitals of the carbon atoms. Cyclopropane shows evidence of delocalisation and is reactive towards typical electrophilic reagents.[85] The quasi-sp^2 hybridisation of the carbon atoms in the three-membered ethylenimine ring in (22c) (compared with the classical sp^3 hybridised carbon atoms of the N,N-dimethylamino group) is probably the predominating factor in determining the overall difference in electron-donating ability of these two groups with respect to the phosphoryl centre, hence responsible for the observed difference in nucleophilic cleavage.

CHAPTER SEVEN

EXPERIMENTAL

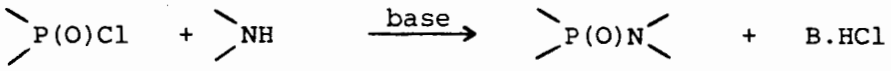
7.1 GENERAL

^{1}H n.m.r. spectra were recorded on a 100 MHz Varian XL100 spectrometer using tetramethylsilane (TMS) as an internal standard. Melting points (uncorrected) were recorded on a Fisher-Johns melting point apparatus. Aluminium-backed silica gel plates (Merck, Kieselgel 60 F_{254} Art. 5554) were used for thin layer chromatography. Column chromatography was carried out on silica gel columns (Merck, Kieselgel 60, 70 - 230 mesh ASTM). Mass spectra were recorded by Miss B.K. Williamson on a VG Micromass 16F spectrometer. Analyses for C, H and N were carried out by Mr W.R.T. Hemsted at the University of Cape Town.

7.1.1 REAGENTS AND SOLVENTS

All solvents were dried by conventional means before use. Pet. ether refers to the fraction of petroleum ether boiling between 60 and 90 °C. Methylamine was dried by passing it through a Drechsel bottle containing NaOH pellets. The remaining amines were distilled from KOH pellets before use. β-Chloroethylammonium chloride and β-bromoethylammonium bromide were ground to a fine powder and dried under vacuum to constant weight over P_2O_5. NaH (Merck) was supplied as a dispersion in paraffin oil. The oil was removed by suspending the required quantity of NaH as supplied in an inert solvent such as benzene, ether or THF. The mixture was swirled and the solid was allowed to settle. The solvent containing the oil was decanted and the NaH was covered immediately with a fresh portion of solvent. This procedure was repeated. The NaH was then suspended in the solvent to be used for the reaction. All operations were carried out under nitrogen. The following reagents were distilled immediately before use: PCl_3, $POCl_3$, $(MeO)_2P(O)Cl$, $(EtO)_2P(O)Cl$, $Et_2P(O)Cl$, $Ph_2P(O)Cl$, $PhOP(O)Cl_2$, $(PhO)_2P(O)Cl$, $SOCl_2$, SO_2Cl_2, $HOCH_2CH_2Cl$ and $ClCH_2CH_2OP(O)Cl_2$.

7.1.2 GENERAL EXPERIMENTAL METHOD FOR THE SYNTHESIS OF PHOSPHORAMIDATES



For (15) and (16) 2 moles of triethylamine were used as a base since β-chloroethylamine was available only as a salt. For other phosphoramidates, *e.g.* (11), (18), (21) and (37), two moles of amine were used; one as a reagent and one as a base. In the case of methylamine, the gas was bubbled into a solution of $\rangle$P(O)Cl for several hours and the mixture was stirred overnight with an excess of the amine.

The general experimental method for (11), (18), (21) and (37) was as follows: The phosphorochloridate in ether was stirred and heated under reflux. Two equivalents of the amine in ether were added dropwise to the solution with protection from moisture. A dense white precipitate formed. The mixture was heated under reflux for several hours and stirred at room temperature overnight. After filtration on a Buchner funnel the solvent was removed under reduced pressure to yield the crude product which was purified by distillation, recrystallisation or column chromatography.

7.2 ACID-BASE BEHAVIOUR OF PHOSPHORAMIDATES

7.2.1 SYNTHESIS OF PHOSPHORAMIDATES (11) and (37)

$(EtO)_2P(O)NMe_2$ (11a) was prepared from diethylphosphorochloridate (Merck) and an excess of dimethylamine in ether. Yield (48%), b.p. 58 °C/0.6 mm (lit.[86] b.p. 84 °C/12 mm), δ ($CDCl_3$) 4.17 - 3.87 (4H, m, α-CH_2), 2.71 (6H, d, $J_{H,P}$ 10 Hz, NMe_2) and 1.32 (6H, t, $J_{H,H}$ 7 Hz, β-CH_3).

$(EtO)_2P(O)NMePh$ (11b) was prepared from diethylphosphorochloridate and two equivalents of N-methylaniline in ether. Yield (40%), b.p. 131 °C/0.6 mm (lit.[87] b.p. 91 - 92 °C/1 mm), δ ($CDCl_3$) 7.30 - 7.22 (5H, m, Ph), 4.25 - 3.88 (4H, m, α-CH_2), 3.19 (3H, d, $J_{H,P}$ 9 Hz, NMe) and 1.26 (6H, t, $J_{H,H}$ 7 Hz, β-CH_3).

(37) was prepared from 5,5-dimethyl-2-chloro-1,3,2-dioxaphosphorinan-2-one[88] and excess dimethylamine in ether and purified by recrystallisation from pet. ether-dichloromethane m.p. 99.5 - 100.5 °C. δ ($CDCl_3$) 4.08 (2H, d of d, $J_{H,P}$ 4.5 Hz and $J_{H_cH_t}$ 11 Hz, H_c), 3.78 (2H, d of d, $J_{H,P}$ 20 Hz and $J_{H_tH_c}$ 11 Hz, H_t), 2.75 (6H, d, $J_{H,P}$ 11 Hz, NMe_2), 1.23 (3H, s, *cis*-Me) and 0.89 (3H, s, *trans*-Me). (Found: C, 43.30; H, 8.51; N, 7.23; P, 15.84. $C_7H_{16}NO_3P$ requires C, 43.52; H, 8.35; N, 7.25; P, 16.03%).*

7.2.2 DETERMINATION OF MEDIUM-INDUCED SHIFTS IN THE ^1H N.M.R. SPECTRA OF (11), (33) AND (37)

Titanium(IV) chloride (Aldrich) and trifluoromethanesulphonic acid HTFMS, (Aldrich) were distilled immediately before use and protected from moisture. Triethyl phosphate (33) (Aldrich) was purified by distillation. δ ($CDCl_3$) 4.22 - 3.95 (6H, m, α-CH_2) and 1.35 (9H, t, $J_{H,H}$ 7 Hz, β-CH_3).
^1H n.m.r. chemical shifts were determined using 5% (w/v) solutions of substrate in the relevant solvent. For spectra of the precursors and their titanium(IV) complexes Silanor-C chloroform-d_1 (Merck) was used as both solvent and lock;

*Elemental analysis determined by Galbraith Laboratories Inc., Knoxville, Tennessee.

for measurements in HTFMS a capillary containing D_2O was used as a lock. Solutions of the complexes were prepared by adding the required amount (3 mol equivalents) of titanium(IV) chloride to a solution of the substrate in chloroform with exclusion of moisture. Solutions in HTFMS were prepared immediately before measurements and the spectra were recorded within 4 - 5 minutes after dissolving a substrate.

7.3 NUCLEOPHILICITY OF THE PHOSPHORAMIDATE FUNCTION

7.3.1 SYNTHESIS OF PHOSPHOROCHLORIDATES, PHOSPHINIC CHLORIDES, PHOSPHORAMIDATES (15), (16), (17b), (18Aa), (18Ba), (21), (22), (50) AND (54) AND THE ESTER (17a)

$(MeO)_2P(O)Cl$

0.5 mol PCl_3 in 44 ml benzene was added dropwise to a stirred solution of 1.5 mol methanol in 150 ml benzene at 8 - 10 °C. 0.5 mol SO_2Cl_2 was added without isolation of the dimethyl phosphite. The mixture was left to stand overnight. The benzene was removed under reduced pressure and the remaining product was purified by distillation to give $(MeO)_2P(O)Cl$ (78%), b.p. 25 - 26 °C/0.03 mm (lit.[89] b.p. 80 °C/18 mm).

$Et_2P(O)Cl$

(1) A solution of 0.177 mol $PSCl_3$ in 35 ml ether was added dropwise, with stirring and cooling, to a solution of Grignard reagent prepared from 0.522 mol Mg and 0.518 mol EtBr in 175 ml ether. The rate of addition was adjusted to maintain the temperature at 10 - 15 °C. The mixture was stirred at room temperature overnight and then heated under reflux on a water bath for 1 hour. 50 ml 10% H_2SO_4 was added slowly to the cooled reaction mixture and the ether layer was separated and dried over anhydrous

Na_2SO_4. Removal of the solvent gave a white solid which was washed with small portions of ice-cold MeOH and dried to give $(Et_2PS)_2$ (55%), m.p. 73 - 74 °C (lit.[90] 76 - 77 °C).

(2) 0.147 mol SO_2Cl_2 in 25 ml benzene was added dropwise with stirring at room temperature to 0.048 mol $(Et_2PS)_2$ in 35 ml benzene. The mixture was stirred for 1 hour. The solution was decanted from the precipitated sulfur, and the benzene, $SOCl_2$ and SO_2 were removed under reduced pressure. The product was purified by distillation to give $Et_2P(O)Cl$ (77%), b.p. 52 - 56 °C/0.15 mm (lit.[91] 64 °C/0.5 mm).

$Ph_2P(O)Cl$

0.053 mol Ph_2PO_2H (Aldrich) and 0.30 mol $SOCl_2$ were mixed together and heated under reflux for 45 minutes. The reaction flask was then attached to a water pump and heated at 120 °C for 3 hours to remove the HCl and SO_2 produced. The pale yellow liquid was purified by distillation to give $Ph_2P(O)Cl$ (65%), b.p. 182 - 184 °C/0.8 mm (lit.[92] 160 - 162 °C/0.15 mm.

$(MeO)(MeNH)P(O)NHCH_2CH_2Cl$ (15a)

$$POCl_3 + ClCH_2CH_2NH_2.HCl \xrightarrow{(a)} Cl_2P(O)NHCH_2CH_2Cl \xrightarrow{(b)}$$

$$Cl(MeO)P(O)NHCH_2CH_2Cl \xrightarrow{(c)} (15a)$$

(a) A mixture of 0.3 mol 2-chloroethylammonium chloride and 1.17 mol phosphorus oxychloride was heated under reflux with stirring for 16 hours. Excess phosphorus oxychloride was removed under reduced pressure and the product was purified by distillation to give $Cl_2P(O)NHCH_2CH_2Cl$ (42%), b.p. 114 - 116 °C/0.5 mm. (Found: C, 12.3; H, 2.5; N, 7.2. $C_2H_5Cl_3NOP$ requires C, 12.23; H, 2.57; N, 7.13%).

(b) 0.03 mol methanol in 5 ml ether and 0.03 mol triethylamine in 5 ml ether were added simultaneously from separate dropping funnels to a stirred and refluxing solution of 0.03 mol $Cl_2P(O)NHCH_2CH_2Cl$ in 50 ml ether. A dense white precipitate formed. The mixture was stirred and heated under reflux for a further 5 hours and then stirred at room temperature for 16 hours. After filtering the reaction mixture and removing the solvent under reduced pressure, crude $Cl(MeO)P(O)NHCH_2CH_2Cl$ was obtained in 88% yield as a viscous liquid and was identified by its ^1H n.m.r. spectrum, δ ($CDCl_3$) 4.60 (1H, br.s, NH), 3.89 (3H, d, $J_{H,P}$ 11 Hz, OMe) and 3.92 - 3.59, 3.53 - 3.23 (4H, m, NCH_2CH_2Cl). This product was used in the next step without further purification.

(c) Dry methylamine was passed through a stirred solution of 0.025 mol $Cl(MeO)P(O)NHCH_2CH_2Cl$ in 50 ml benzene. After saturating the mixture with methylamine (2 - 3 hours) the benzene was removed under reduced pressure and chloroform was added to the crude product. Methylammonium chloride was filtered off and the chloroform was removed under reduced pressure. The crude product was purified by column chromatography using acetone/chloroform (1:3) as eluant to give (15a) (39%), δ ($CDCl_3$) 3.67 (3H, d, $J_{H,P}$ 11 Hz, OMe), 3.62 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl), 3.42 - 3.14 (3H, m, $NHCH_2$) and 2.61 (3H, d of d, $J_{H,H}$ 6 Hz and $J_{H,P}$ 13 Hz, NMe). (Found: C, 25.9; H, 6.15; N, 12.6. $C_4H_{12}ClN_2O_2P$ requires C, 25.75; H, 6.48; N, 15.02%). Multiple analyses gave the same result. (15a) was chromatographically homogeneous and the ^1H n.m.r. spectrum was in full agreement with that predicated for this compound.

(PhO)(MeNH)P(O)NHCH$_2$CH$_2$Cl (15b)

$$PhOP(O)Cl_2 + ClCH_2CH_2NH_2.HCl \xrightarrow{(a)} Cl(PhO)P(O)NHCH_2CH_2Cl \xrightarrow{(b)} (15b)$$

(a) 0.2 mol triethylamine in 100 ml ether was added dropwise to a stirred and refluxing solution of 0.1 mol PhOP(O)Cl$_2$ (Merck) and 0.1 mol 2-chloroethylammonium chloride in 200 ml ether. A dense, white precipitate formed. The mixture was stirred and heated under reflux for 5 hours and then stirred at room temperature for 16 hours. Filtration and removal of the solvent gave Cl(PhO)P(O)NHCH$_2$CH$_2$Cl as a pale brown oil, (84%), δ ($CDCl_3$) 7.46 - 7.12 (5H, m, Ph) and 3.71 - 3.20 (5H, m, NHCH$_2$CH$_2$Cl). This product was used in the next step without purification.

(b) Dry methylamine was passed through a stirred solution of 0.16 mol Cl(PhO)P(O)NHCH$_2$CH$_2$Cl in 200 ml benzene. The mixture was stirred with an excess of methylamine for 16 hours, filtered, and the solvent was removed under reduced pressure. The crude product was purified by column chromatography using ethyl acetate as eluant to give (15b) (45%), δ ($CDCl_3$) 7.36 - 7.09 (5H, m, Ph), 3.55 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl), 3.42 - 3.20 (3H, m, $NHCH_2$) and 2.63 (3H, d of d, $J_{H,H}$ 5 Hz and $J_{H,P}$ 15 Hz, NMe). (Found: C, 43.4; H, 5.7; N, 11.2. $C_9H_{14}ClN_2O_2P$ requires C, 43.47; H, 5.67; N, 11.27%).

(MeO)$_2$P(O)NHCH$_2$CH$_2$Cl (16a)

$$(MeO)_2P(O)Cl + ClCH_2CH_2NH_2.HCl \xrightarrow[\text{ether}]{Et_3N} (16a)$$

0.2 mol dimethylphosphorochloridate and 0.24 mol 2-chloroethylammonium chloride were heated under reflux with stirring in 250 ml ether. 0.48 mol triethylamine in 75 ml ether was added dropwise. The mixture was then heated under reflux for 7 hours and stirred at room temperature overnight. After

filtering the reaction mixture and removing the solvent under reduced pressure, the product was purified by distillation to give (16a) (73%), b.p. 130 °C/ 1 mm, δ ($CDCl_3$) 3.74 (6H, d, $J_{H,P}$ 12 Hz, OMe), 3.68 (2H, t, $J_{H,H}$ 5 Hz, CH_2Cl) and 3.40 – 3.14 (3H, m, $NHCH_2$). (Found: C, 25.6; H, 6.0; N, 7.5. $C_4H_{11}ClNO_3P$ requires C, 25.61; H, 5.91; N, 7.47%).

$(PhO)_2P(O)NHCH_2CH_2Cl$ (16b)

$$(PhO)_2P(O)Cl + ClCH_2CH_2NH_2.HCl \xrightarrow[ether]{Et_3N} (16b)$$

(16b) was prepared from $(PhO)_2P(O)Cl$ and 2-chloroethylammonium chloride according to the method described for (16a). The oil obtained solidified on standing to give (16b) (96%), m.p. 34 - 37 °C, δ ($CDCl_3$) 7.14 - 6.78 (10H, m, 2XPh), 3.55 - 3.40 (1H, br.s, NH) and 3.22 – 2.98 (4H, m, NCH_2CH_2Cl). (Found: C, 53.85; H, 4.95; N, 4.7. $C_{14}H_{15}ClNO_3P$ requires C, 53.94; H, 4.85; N, 4.47%).

$Et_2P(O)NHCH_2CH_2Cl$ (16c)

$$Et_2P(O)Cl + ClCH_2CH_2NH_2.HCl \xrightarrow[ether]{Et_3N} (16c)$$

(16c) was prepared from $Et_2P(O)Cl$ and 2-chloroethylammonium chloride according to the method described for (16a). The crude product was purified by column chromatography using acetone as eluant to give (16c) (31%), δ ($CDCl_3$) 3.65 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl), 3.48 - 3.18 (2H, m, NCH_2), 3.18 - 2.80 (1H, m, NH), 1.96 - 1.53 (4H, m, α-CH_2) and 1.16 (6H, d of t, $J_{H,H}$ 8 Hz and $J_{H,P}$ 18 Hz, β-CH_3). (Found: C, 39.55; H, 8.15; N, 6.9. $C_6H_{15}ClNOP$ requires C, 39.24; H, 8.23; N, 7.63%).

$Ph_2P(O)NHCH_2CH_2Cl$ (16d)

$$Ph_2P(O)Cl + ClCH_2CH_2NH_2.HCl \xrightarrow[benzene]{Et_3N} (16d)$$

(16d) was prepared from $Ph_2P(O)Cl$ and 2-chloroethylammonium chloride in benzene according to the method described for (16a). The crude product was purified by recrystallisation from CCl_4 to give (16d) (74%), m.p. 98 - 100 °C, δ ($CDCl_3$) 8.02 - 7.80 and 7.58 - 7.40 (10H, m, 2XPh), 3.67 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl), 3.41 - 3.19 (2H, m, NCH_2) and 3.19 - 2.90 (1H, br.s, NH). (Found: C, 60.0; H, 5.35; N, 5.0. $C_{14}H_{15}ClNOP$ requires C, 60.12; H, 5.40; N, 5.01%).

$(MeO)_2P(O)OCH_2CH_2Cl$ (17a)

$$POCl_3 + ClCH_2CH_2OH \xrightarrow{(a)} ClCH_2CH_2OP(O)Cl_2 \xrightarrow{(b)} (17a)$$

(a) 0.25 mol $POCl_3$ was dissolved in 45 ml ether. 0.25 mol $ClCH_2CH_2OH$ was added dropwise with stirring at 0 °C. The mixture was heated under reflux for 4 hours. The solvent was removed under reduced pressure to afford $ClCH_2CH_2OP(O)Cl_2$ which was purified by distillation (57%), b.p. 110 - 114 °C/18 mm, δ ($CDCl_3$) 4.65 - 4.43 (2H, m, OCH_2) and 3.80 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl).

(b) To a refluxing solution of 0.05 mol $ClCH_2CH_2OP(O)Cl_2$ in 50 ml ether, solutions of 0.1 mol triethylamine in 20 ml ether and 0.1 mol methanol in 20 ml ether were added simultaneously from separate dropping funnels. A dense white precipitate formed. The mixture was heated under reflux for 3 hours and left to stand overnight at room temperature. Filtration and removal of the solvent under reduced pressure followed by distillation of the residue afforded the product (17a) (44%), b.p. 80 - 82 °C/0.2 mm, δ ($CDCl_3$) 4.39 - 4.18 (2H, m, OCH_2), 3.82 (6H, d, $J_{H,P}$ 11 Hz, OMe) and

3.90 - 3.68 (2H, m, CH_2Cl). (Found: C, 25.2; H, 5.35. $C_4H_{10}ClO_4P$ requires C, 25.48; H, 5.35%).

(MeO)(MeNH)P(O)OCH_2CH_2Cl (17b)

$ClCH_2CH_2OP(O)Cl_2 \xrightarrow{(a)} ClCH_2CH_2OP(O)(OMe)Cl \xrightarrow{(b)}$ (17b)

(a) 0.06 mol methanol in 20 ml ether and 0.06 mol triethylamine in 20 ml ether were added simultaneously from separate dropping funnels to a refluxing solution of 0.06 mol $ClCH_2CH_2OP(O)Cl_2$ in 20 ml ether. The mixture was heated under reflux for a further 5 hours and stirred at room temperature overnight. After filtering off the amine hydrochloride and removing the solvent under reduced pressure the crude product was obtained as a mobile liquid (93%), δ ($CDCl_3$) 4.52 - 4.20 (2H, m, OCH_2), 3.94 (3H, d, $J_{H,P}$ 11 Hz, OMe) and 3.76 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl).

(b) 0.055 mol $ClCH_2CH_2OP(O)(OMe)Cl$ was dissolved in 50 ml ether and dry methylamine was passed through the solution at room temperature. A white precipitate formed. After filtering the mixture and removing the solvent the crude product was purified by column chromatography using chloroform as eluant to give (17b) (42%), δ ($CDCl_3$) 4.32 - 4.12 (2H, m, OCH_2), 3.76 (3H, d, $J_{H,P}$ 11 Hz, OMe), 3.86 - 3.66 (2H, m, CH_2Cl), 3.15 (1H, br.s, NH) and 2.63 (3H, d of d, $J_{H,H}$ 6 Hz and $J_{H,P}$ 13 Hz, NMe). (Found: C, 25.6; H, 6.0; N, 7.05. $C_4H_{11}ClNO_3P$ requires C, 25.61; H, 5.91; N, 7.47%).

$(MeO)_2P(O)NHMe$ (18Aa)

Dry methylamine was passed through a stirred solution of 0.086 mol $(MeO)_2P(O)Cl$ in 50 ml ether. The mixture was stirred at room temperature overnight and filtered. Removal of the solvent gave (18Aa) which was purified by distillation. Yield (40%), b.p. 95 - 96 °C/0.5 mm (lit.[93] 81 °C/1 mm), δ ($CDCl_3$) 4.52 - 4.13 (1H, br.s, NH), 3.80 (6H, d, $J_{H,P}$ 11 Hz, OMe) and 2.60 (3H, d of d, $J_{H,H}$ 6 Hz and $J_{H,P}$ 14 Hz, NMe).

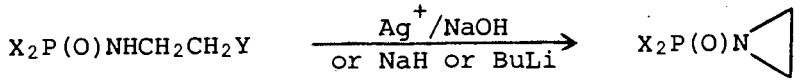
$(PhO)_2P(O)NHMe$ (18Ba)

Dry methylamine was passed through a stirred solution of 0.06 mol $(PhO)_2P(O)Cl$ in 150 ml ether at room temperature. A dense white precipitate formed. The mixture was stirred at room temperature overnight. Filtration and removal of the solvent yielded (18Ba). As the yield was low the filtered $MeNH_2.HCl$ was suspended in a mixture of benzene and chloroform. Filtration and removal of the solvent yielded more (18Ba). The crude product was purified by recrystallisation from benzene to yield (18Ba) (80%), m.p. 93 - 94 °C, δ ($CDCl_3$) 7.40 - 7.17 (10H, m, 2XPh), 3.60 - 3.30 (1H, br.s, NH) and 2.73 (3H, d of d, $J_{H,H}$ 6 Hz and $J_{H,P}$ 14 Hz, NMe). (Found: C, 59.15; H,5.3; N, 5.3. $C_{13}H_{14}NO_3P$ requires C, 59.32; H, 5.36; N, 5.32%).

$(MeO)_2P(O)NMe_2$ (21)

(21) was prepared from $(MeO)_2P(O)Cl$ and dry Me_2NH according to the method described in Chapter 7.1.2. The crude product was purified by distillation to give (21) (62%), b.p. 46 - 48 °C/0.5 mm (lit.[86] 72 - 72.5 °C/11 mm), δ ($CDCl_3$) 3.80 (6H, d, $J_{H,P}$ 11 Hz, OMe) and 2.80 (6H, d, $J_{H,P}$ 10 Hz, NMe).

N-phosphorylated ethylenimines (22)



(16) Y = Cl

(54) Y = Br

The synthetic methods using (1) Ag^+/OH^- (2) NaH and (3) BuLi are described below.

(1) Ag^+/NaOH

0.01 mol substrate was dissolved in water or dioxan and added to an aqueous suspension of silver oxide [prepared from silver nitrate (0.01 mol) and sodium hydroxide] at pH *ca.* 11. The mixture was stirred at 70 °C for 2½ hours and then at room temperature for 16 - 18 hours. At the end of the reaction the pH of the mixture was 7. The mixture was centrifuged, the supernatant liquid was decanted and extracted with chloroform. The extract was dried over anhydrous sodium sulphate and the solvent was removed under reduced pressure. The crude product was purified by distillation, column chromatography or recrystallisation.

(2) NaH

0.01 mol of the substrate in THF was added dropwise under nitrogen to a stirred suspension of 0.011 mol sodium hydride in THF. There was a vigorous evolution of hydrogen and a white precipitate formed. The mixture was heated under reflux for 1 - 2 hours, cooled, filtered and the solvent was removed under reduced pressure. The crude product was purified by distillation, column chromatography or recrystallisation.

(3) BuLi

0.01 mol of the substrate in THF was added dropwise to a hexane-tetrahydrofuran solution of n-butyl-lithium Merck (0.01 mol) and the mixture was heated under reflux for 3 hours. Filtration followed by evaporation of the solvent gave (22a), which was purified by distillation.

$(MeO)_2P(O)N$ (22a)

(1) from $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) and $Ag^+/NaOH$: The product was purified by distillation to give (22a) (40%), b.p. 126 - 128 °C/16 mm (lit.[94] b.p. 99.5 - 100 °C/10 mm), δ ($CDCl_3$) 3.83 (6H, d, $J_{H,P}$ 11 Hz, OMe) and 2.20 (4H, d, $J_{H,P}$ 15 Hz, NC_2H_4). (Found: C, 31.6; H, 6.75; N, 8.5. Calc. for $C_4H_{10}NO_3P$: C, 31.79; H, 6.67; N, 9.27%).

(2) from (16a) and NaH: (22a) was purified by distillation (70%).

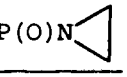
(3) from (16a) and BuLi: (22a) was purified by distillation (43%).

(4) from $(MeO)_2P(O)NHCH_2CH_2Br$ (54) and Ag^+/OH^-: (22a) was purified by distillation (43%).

$Et_2P(O)N$ (22b)

(1) from $Et_2P(O)NHCH_2CH_2Cl$ (16c) and $Ag^+/NaOH$: (83%). The product was identified by its ^1H n.m.r. spectrum, δ ($CDCl_3$) 2.14 (4H, d, $H_{H,P}$ 14 Hz, NC_2H_4), 1.98 - 1.46 (4H, m, α-CH_2) and 1.12 (6H, d of t, $J_{H,H}$ 8 Hz and $J_{H,P}$ 18 Hz, β-CH_3).

(2) from (16c) and NaH: (69%). The product was identified by its ^1H n.m.r. spectrum.

$Ph_2P(O)N$  (22c)

(1) from $Ph_2P(O)NHCH_2CH_2Cl$ (16d) and NaH: The product was purified by recrystallisation from acetone and hexane (87%) m.p. 120.5 - 121.5 °C (lit.[74] 119 - 119.5 °C from hexane), δ ($CDCl_3$) 8.18 - 7.70 and 7.65 - 7.36 (10H, m, 2XPh) and 2.29 (4H, d, $J_{H,P}$ 15 Hz, NC_2H_4). (Found: C, 68.9; H, 5.75; N, 5.7. Calc. for $C_{14}H_{14}NOP$: C, 69.13; H, 5.80; N, 5.76%).

(2) from (16d) and Ag^+/NaOH: (29%). The product was identified by its ^1H n.m.r. spectrum.

$(PhO)_2P(O)N$  (22d)

(1) from $(PhO)_2P(O)NHCH_2CH_2Cl$ (16b) and Ag^+/NaOH: (16b) was treated with $AgNO_3$ and NaOH as described. The mixture of products obtained from this reaction was identified by its ^1H n.m.r. spectrum as (16b) (51%), $(PhO)_2P(O)N$  (22d) (17%), δ ($CDCl_3$) 7.40 - 7.05 (10H, m. 2XPh) and 2.35 (4H, d, $J_{H,P}$ 15 Hz, NC_2H_4), and phenol (32%).

(2) from (16b) and NaH: (16b) was treated with NaH as described for (16a). The mixture of products obtained from this reaction was identified by its ^1H n.m.r. spectrum as (22d) (7.5%), the rest of the mixture comprising (16b) and phenol. The phenol was characterised by reaction with bromine to form 2,4,6-tribromophenol as described in the reaction of $(PhO)_2P(O)NHMe$ (18Ba) with NaH (see Chapter 7.3.2).

(3) from (16b) and BuLi: (16b) was treated with BuLi as described for (16a). A complex mixture of products was obtained. No (22d) was formed as shown by ^1H n.m.r.

(MeO)(MeNH)P(O)N△ (50a)

(1) from (MeO)(MeNH)P(O)NHCH$_2$CH$_2$Cl (15a) and Ag^+/OH^-: (15a) was treated with silver oxide in aqueous dioxan as described for (16). The reaction mixture was heated under reflux for 24 hours before isolation of the product. The ethylenimine derivative (50a) was obtained together with unreacted starting material. The yield of (50a) was 39% as estimated from the ratio of the NCH_2CH_2 protons of (15a) relative to those of the ethylenimine ring in (50a). The ethylenimine derivative was identified by its ^{1}H n.m.r. spectrum; δ ($CDCl_3$) 3.70 (3H, d, $J_{H,P}$ 11 Hz, OMe), 2.68 (3H, d of d, $J_{H,H}$ 5 Hz and $J_{H,P}$ 15 Hz, NMe) and 2.12 (4H, d, $J_{H,P}$ 16 Hz, NC_2H_4).

(2) from (15a) and NaH: (15a) was treated with NaH in THF as described for (16). (50a) was identified by its ^{1}H n.m.r. spectrum and the yield of N-phosphorylated ethylenimine was 45%.

(PhO)(MeNH)P(O)N△ (50b)

(1) from (PhO)(MeNH)P(O)NHCH$_2$CH$_2$Cl (15b) and Ag^+/OH^-: (15b) was treated with silver oxide in aqueous dioxan as described for (16). The reaction mixture was heated under reflux for 24 hours before isolation of the product. (50b) was obtained together with unreacted starting material. The yield of (50b) was 70% and it was identified by its ^{1}H n.m.r. spectrum; δ ($CDCl_3$) 7.23 - 7.00 (5H, m, Ph), 2.67 (3H, d of d, $J_{H,H}$ 5 Hz and $J_{H,P}$ 15 Hz, NMe) and 2.17 (4H, d, $J_{H,P}$ 16 Hz, NC_2H_4).

(2) from (15b) and NaH: (15b) was treated with NaH in THF as described for (16). The crude reaction mixture obtained was estimated (by ^{1}H n.m.r.) to consist of unreacted (15b), the required ethylenimine derivative (50b)

and phenol in the ratio 6 : 14 : 5. The crude reaction mixture was divided into two portions. One of these was acidified with 5% H_2SO_4 and treated with bromine as described for $(PhO)_2P(O)NHMe$ (18Ba) (see Chapter 7.3.2). 2,4,6-Tribromophenol corresponding to 15% of the original reaction mixture was isolated. An attempt to purify the crude N-phosphorylated ethylenimine (50b) in the other portion of the reaction mixture by column chromatography using chloroform/ethyl acetate (1 : 1) as eluant was unsuccessful as (50b) decomposed and only phenol was isolated.

$(MeO)_2P(O)NHCH_2CH_2Br$ (54)

$$(MeO)_2P(O)Cl + BrCH_2CH_2NH_2.HBr \xrightarrow[ether]{Et_3N} (54)$$

(54) was prepared from $(MeO)_2P(O)Cl$ and 2-bromoethylammonium bromide according to the method described for (16a). The crude product was purified by column chromatography using ethyl acetate as eluant to give (54) (52%), δ ($CDCl_3$) 3.73 (6H, d, $J_{H,P}$ 11 Hz, OMe), 3.47 - 3.37 (2H, m, CH_2Br) and 3.34 - 3.18 (2H, m, NCH_2). (Found: C, 21.6; H, 4.95; N, 5.55. $C_4H_{11}BrNO_3P$ requires C, 21.73; H, 4.78; N, 6.03%).

7.3.2 REACTIONS DISCUSSED IN CHAPTER THREE

The reaction of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) with NaH and MeI

(1) using excess MeI

5.3 mmol (16a) in 2 ml THF was added in one portion to a stirred suspension of 5.3 mmol NaH and 27 mmol MeI in 5 ml THF under nitrogen. Vigorous evolution of hydrogen was observed and the mixture became warm. The mixture was stirred at room temperature for 2 hours. Filtration and removal of the solvent gave a mixture consisting of 7% $(MeO)_2P(O)N$ (22a)

and 93% $(MeO)_2P(O)N(Me)CH_2CH_2Cl$ (58). The mixture was identified from its ^1H n.m.r. spectrum which showed the absence of any substrate and by addition of authentic (22a). δ ($CDCl_3$) for (22a) 3.83 (6H, d, $J_{H,P}$ 11 Hz, OMe) and 2.20 (4H, d, $J_{H,P}$ 16 Hz, NC_2H_4), and for (58) 3.76 (6H, d, $J_{H,P}$ 11 Hz, OMe), 3.68 (2H, t, $J_{H,H}$ 6 Hz, CH_2Cl), 3.50 - 3.34 (2H, m, NCH_2) and 2.76 (3H, d, $J_{H,P}$ 10 Hz, NMe).

(2) using equimolar quantities of (16a) and MeI and varying volumes of THF

A mixture of 2 mmol (16a) and 2 mmol MeI in 10 ml THF was added in one portion to a stirred suspension of 2 mmol NaH in THF. The reaction was repeated three times while varying the total volume of THF used from 20 to 60 ml. The mixtures were stirred at room temperature for two hours. Filtration and removal of the solvent yielded an oil consisting of (22a) and (58). These were identified as described above. The relative amounts of (22a) and (58) were estimated from the ratio of the integrated height of the hydrogens of the ethylenimine ring of (22a), *i.e.* doublet at δ 2.20, relative to those of the N-methyl doublet of (58) at δ 2.76. These integrated heights were statistically corrected to the number of hydrogens present. The results are shown in Table 3 (see Chapter 3.2.2).

Solvolysis of $(MeO)_2P(O)OCH_2CH_2Cl$ (17a)

The ester (17a) was treated with silver oxide in deuterium oxide as described for (16a). After removal of the silver salt by centrifugation the ^1H n.m.r. spectrum of the reaction mixture showed that more than 90% of the substrate remained unchanged and that deuteriomethanol (*ca.* 4%) was formed (δ 3.34, s, identified by addition of authentic material). A similar proportion of deuteriomethanol was formed when (17a) was heated in deuterium oxide without silver oxide and when trimethyl phosphate was heated in deuterium oxide at 60 - 70 °C for 24 hours.

The reaction of $(MeO)(MeNH)P(O)OCH_2CH_2Cl$ (17b) with NaH

0.01 mol (17b) in 40 ml ether was added dropwise to a stirred suspension of 0.02 mol NaH in 10 ml ether. The mixture was heated under reflux for 5 hours and then stirred at room temperature overnight. After neutralisation with CF_3COOH the solvent was removed to yield > 90% (17b), which was identified by its ^1H n.m.r. spectrum.

The reaction of $(MeO)(MeNH)P(O)OCH_2CH_2Cl$ (17b) with NaH and MeI

2 mmol (17b) and 2 mmol MeI were dissolved in 10 ml THF and added to a stirred suspension of 2 mmol NaH in 10 ml THF. There was a vigorous evolution of hydrogen. The mixture was stirred at room temperature for 2 hours, filtered, and the solvent was removed to yield 70% $(MeO)(Me_2N)P(O)OCH_2CH_2Cl$ (62), δ ($CDCl_3$) 4.30 - 4.08 (2H, m, OCH_2), 3.70 (3H, d, $J_{H,P}$ 11 Hz, OMe), 3.86 - 3.64 (2H, m, CH_2Cl) and 2.63 (6H, d, $J_{H,P}$ 11 Hz, NMe).

The reaction of $(MeO)_2P(O)NHMe$ (18Aa) with NaH and MeI

0.002 mol (18Aa) in 2 ml THF was added in one portion to a stirred suspension of 0.002 mol NaH and 0.01 mol MeI in 5 ml THF. A vigorous evolution of hydrogen was observed and the mixture became warm. The mixture was stirred at room temperature for 2 hours and left to settle overnight. Filtration and removal of the solvent gave $(MeO)_2P(O)NMe_2$ (21) (72%). (21) was identified by its ^1H n.m.r. spectrum and by addition of authentic material prepared from $(MeO)_2P(O)Cl$ and Me_2NH.

The reaction of $(EtO)_2P(O)NHMe$ (18Au) with NaH

(a) at room temperature:

0.020 mol (18Au) (prepared in this laboratory by V. Mizrahi) in 10 ml THF was added dropwise to a stirred suspension of 0.022 mol NaH in THF.

There was a vigorous evolution of hydrogen. The mixture was stirred at room temperature for two hours and then neutralised with CF_3COOH in methanol. The solvent was removed to yield (18Au) (76%), which was identified by its ^1H n.m.r. spectrum, δ ($CDCl_3$) 4.21 - 3.92 (4H, m, α-CH_2), 3.45 - 3.15 (1H, br.s, NH), 2.59 (3H, d of d, $J_{H,H}$ 6 Hz and $J_{H,P}$ 14 Hz, NMe) and 1.33 (6H, t, $J_{H,H}$ 6 Hz, β-CH_3).

(b) at room temperature with subsequent reflux:

The reaction described in (a) above was repeated. The reaction mixture was heated under reflux for 1 hour, cooled and neutralised with CF_3COOH in methanol. The solvent was removed to yield (18Au) (65%), which was identified by its ^1H n.m.r. spectrum.

The reaction of $(PhO)_2P(O)NHMe$ (18Ba) with NaH

0.01 mol (18Ba) was dissolved with warming in 10 ml benzene and added dropwise to a stirred suspension of 0.015 mol NaH in benzene under nitrogen. There was a vigorous evolution of hydrogen. The mixture was stirred at room temperature for 2 hours and then acidified with 5% H_2SO_4. The benzene layer was extracted several times with water. Bromine was added to the combined aqueous extracts and a solid precipitated. It was filtered and recrystallised from a large volume of ethanol to yield 2,4,6-tribromophenol (16%), m.p. 91 °C (lit.[75] 95 °C). (Found: C, 22.1; H, 0.9%; M^+ 330 and 332. Calc. for $C_6H_3Br_3O$: C, 21.78; H, 0.91% M^+ 330 and 332). The isolated product had the same R_F as an authentic sample in three different solvents, *viz.* 0.49 in benzene, 0.55 in chloroform and 0.57 in ethyl acetate/hexane (3 : 10).

The reaction of $(MeO)_2P(O)NHCH_2CH_2Br$ (54) with pyridine

A mixture of 0.002 mol (54) and 0.002 mol pyridine in 10 ml benzene was heated under reflux for 4 hours. The solvent was removed under reduced pressure and the crude product was obtained as a viscous oil. The ^1H n.m.r. spectrum of this product showed the absence of any substrate and the presence of the salt, N-methylpyridinium O-methyl-N-(β-bromoethyl)amidophosphate (56), δ (D_2O) 9.14 - 8.80, 8.78 - 8.49, 8.35 - 8.02 (2H, 1H and 2H, respectively, α-, γ- and β-H respectively of $C_5H_5N^+$), 4.46 (3H, s, $\overset{+}{N}Me$), 3.40 (3H, d, $J_{H,P}$ 11 Hz, OMe) and 3.60 - 3.14 (4H, m, NCH_2CH_2Br). Signals of the N-methylpyridinium cation of (56) were identical with those observed for an authentic sample of N-methylpyridinium iodide.

7.4 ELECTRON IMPACT-INDUCED FRAGMENTATION PATHWAYS OF PHOSPHORAMIDATES

7.4.1 SYNTHESIS OF THE PHOSPHORAMIDATES

The preparation of those substrates used solely for the determination of their mass spectra is described in Chapter 7.4.1.

The syntheses of the phosphoramidates (15), (16), (17), (18Aa), (18Ba), (21) and (22) were described in Chapter 7.3.1.

Most of the substrates studied were prepared according to prepared according to procedures reported before: (18Ae-m);[25] (18An-r);[95] (18Ad) and (18Bc-g);[96] (18Av);[97] (18Bh).[98] In all cases the yields were satisfactory (60 - 80%) and the samples were chromatographically (TLC) homogeneous. The ^1H n.m.r. spectra in deuteriated chloroform, using tetramethylsilane as an internal standard, were in full agreement with those predicted for the compounds.

$(MeO)_2P(O)NHEt$ (18Ab) was prepared from dimethylphosphorochloridate and two equivalents of ethylamine in ether (78%), b.p. 88 °C/0.5 mm, δ ($CDCl_3$)

3.72 (6H, d, $J_{H,P}$ 11 Hz, OMe), 3.18 - 2.82 (3H, m. $NHCH_2$) and 1.17 (3H, t, $J_{H,H}$ 6 Hz β-Me). (Found: C, 31.2; H, 7.75; N, 9.0. $C_4H_{12}NO_3P$ requires C, 31.37; H, 7.90; N, 9.15%).

$(MeO)_2P(O)NHCHMe_2$ (18Ac) was prepared from dimethylphosphorochloridate and two equivalents of 2-aminopropane in ether. (18Ac) crystallised spontaneously after distillation (56%), m.p. 36 - 38 °C, δ ($CDCl_3$) 3.67 (6H, d, $J_{H,P}$ 11 Hz, OMe), 3.80 - 3.10 (2H, m, NHCH) and 1.15 (6H, d, $J_{H,H}$ 6 Hz, CMe_2). (Found: C, 35.75; H, 8.5; N, 8.3. $C_5H_{14}NO_3P$ requires C, 35.93; H, 8.44; N, 8.38%).

(18As,t) were prepared from dimethyl-d_6-phosphorochloridate [synthesised from PCl_3 and methanol-d_4 (Wilmad Glass Co.) according to ref. 89; 78%, b.p. 34 °C/ 0.5 mm] and two equivalents of the corresponding amine in ether, and purified by recrystallisation from benzene and pet. ether.

$(CD_3O)_2P(O)NHPh$ (18As) (54%), m.p. 85 - 87 °C. (Found: C, 45.95; H + D, 8.9; N, 7.0. $C_8H_6D_6NO_3P$ requires C, 46.39; H + D, 8.72; N, 6.76%).

$(CD_3O)_2P(O)NHC_6H_4Me$-4 (18At) (55%), m.p. 114 - 115 °C. (Found: C, 48.9; H + D, 9.3; N, 6.4. $C_9H_8D_6NO_3P$ requires C, 48.88; H + D, 9.07; N, 6.34%).

$(MeO)_2P(O)NDPh$ (18Aw) was prepared by dissolving $(MeO)_2P(O)NHPh$ (18Ae) in excess methanol-d_4 and this solution was used for the mass spectral determination.

$(PhO)_2P(O)NHEt$ (18Bb) was prepared from diphenylphosphorochloridate (Merck) and two equivalents of ethylamine in ether and was purified by recrystallisation from benzene and pet. ether (91%), m.p. 49 - 50 °C, δ ($CDCl_3$) 7.30 - 7.20 (10H, m, 2XPh), 3.65 - 3.40 (1H, m, NH), 3.22 - 2.98 (2H, m, CH_2) and 1.10 (3H, t, $J_{H,H}$ 6 Hz, β-Me). (Found: C, 60.85; H, 5.9; N, 5.15. $C_{14}H_{16}NO_3P$ requires C, 60.65; H, 5.82; N, 5.05%).

$(PhO)_2P(O)NMe_2$ (18Bi) was prepared by N-methylation of $(PhO)_2P(O)NHMe$ (18Ba). A solution of 0.009 mol of (18Ba) and 0.015 mol MeI in THF was added to a stirred suspension of 0.009 mole of NaH in THF. The mixture was stirred at room temperature for two hours, filtered, and the solvent was evaporated *in vacuo*. The residue was dissolved in chloroform, filtered and the solvent evaporated under reduced pressure. The remaining oil was purified by column chromatography using chloroform/acetone (95 : 5) as eluant to afford (18Bi) (35%), δ ($CDCl_3$) 7.40 – 7.30 (10H, m, 2XPh) and 2.83 (6H, d, $H_{H,P}$ 12 Hz, NMe_2). (Found: C, 60.1; H, 5.75; N, 4.75. $C_{14}H_{16}NO_3P$ requires C, 60.65; H, 5.82; N, 5.05%).

$PhNHCD_3$ (79b). Equimolar amounts of aniline and iodomethane-d_3 (Merck) were stirred together at room temperature for 2 hours and then heated under reflux for a further 2 hours. After filtration the liquid product was separated by preparative TLC using pet. ether/ethyl acetate (9 : 1) as eluant. The fraction which showed a peak at m/e = 110 (molecular ion) in the mass spectrum was identified as (79b).

7.4.2 DETERMINATION OF THE MASS SPECTRA

The mass spectra were recorded on a VG Micromass 16F spectrometer at 70 eV and an ion source temperature between 180 and 220 °C. A direct probe introduction system operating at ambient temperature was used. The low-energy (11 eV) spectrum of (15b) was also recorded on this instrument.
The exact mass measurements of (18Ba) were obtained at Potchefstroom University on a VG Micromass 70-70E spectrometer (with extended geometry). The analyses were done at 70 eV and a resolving power of 10 000 using PFK as an internal standard. The source temperature was 200 °C.

The exact mass measurements of m/e 155 in (15b) were obtained at Stellenbosch University on a Varian MAT 311A spectrometer operating at 70 eV. The resolving power was 7000, the source temperature 175 °C and PFK was used as an internal reference.

7.5 NUCLEOPHILIC CLEAVAGE OF THE ESTER AND AMIDE BONDS IN PHOSPHORAMIDATES

7.5.1 REAGENTS AND SUBSTRATES

Methanol-d_4, (Wilmad Glass Co. Inc. 99.5% D Min) and D_2O (Merck Uvasol 99.75% D Min) were used as supplied. A stock solution of sodium deuteroxide was made by diluting sodium deuteroxide, 40% in D_2O (Wilmad Glass Co. Inc. 99.0% D Min), with D_2O. This solution was standardised by titration with HCl using screened methyl orange as indicator.

$Ph_2P(O)OMe$ (112) was prepared from diphenylphosphinyl chloride and methanol,[99] δ (CD_3OD) 8.15 - 7.53 (10H, m, 2XPh) and 3.77 (3H, d, $J_{H,P}$ 11 Hz, OMe).

$(MeO)_3PO$ (99) (Merck) was distilled prior to use. The syntheses of $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a), $(MeO)_2P(O)NHMe$ (18Aa), $(MeO)_2P(O)NMe_2$ (21), $(MeO)_2P(O)N$⟨ (22a) and $Ph_2P(O)N$⟨ (22c) were described in Chapter 7.3.1.

7.5.2 KINETICS AND PRODUCT DETERMINATION

^1H n.m.r. spectra were determined on a Varian EM 360A spectrometer using D_2O as a solvent and DSS as an internal standard. Cleavage products were identified by addition of authentic samples of sodium dimethyl phosphate [prepared from trimethyl phosphate (99) and aqueous NaOH[100]], methanol, ethylenimine, dimethylammonium chloride, as well as by comparison with the ^1H n.m.r. spectra of mixtures of relevant compounds. The following signals were used to

identify cleavage products and to follow the kinetics of base-catalysed hydrolysis. In all cases the signal arising from the >P(O)OMe moiety was a doublet with $J_{H,P}$ 11 Hz.

$(MeO)_3PO$ (99)

Substrate: δ 3.82, d, OMe

P-O cleavage products: δ 3.58, d, OMe; δ 3.35, s, MeOH

$(MeO)_2P(O)NHMe$ (18Aa)

Substrate: δ 3.80, d, OMe; δ 2.62, d, $J_{H,P}$ 13 Hz, PNMe

P-O cleavage products: δ 3.60, d, OMe; δ 2.50, d, $J_{H,P}$ 13 Hz, PNMe; δ 3.38, s, MeOH

$(MeO)_2P(O)NMe_2$ (21)

Substrate: δ 3.67, d, OMe; δ 2.67, d, $J_{H,P}$ 10 Hz, PNMe

P-O cleavage products: δ 3.51, d, OMe; δ 2.48, d, $J_{H,P}$ 10 Hz, PNMe; δ 3.29, s, MeOH

$(MeO)_2P(O)N\triangleleft$ (22a)

Substrate: δ 3.80, d, OMe; δ 2.30, d, $J_{H,P}$ 14 Hz, PNC_2H_4

P-O cleavage products: δ 3.64, d, OMe; δ 1.98, d, $J_{H,P}$ 14 Hz, PNC_2H_4; δ 3.31, s, MeOH

P-N cleavage products: δ 3.58, d, OMe; δ 1.62, s, $HN\triangleleft$

The substrate (20 - 30 mg) was introduced into an n.m.r. tube which was equilibrated in a water bath at 31 ± 0.5 °C. The solution of sodium deuteroxide was added and the base-catalysed hydrolysis was followed by recording the spectrum at 31 °C (probe temperature). Fast runs ($t_{\frac{1}{2}}$ < 30 minutes) were followed by placing the n.m.r. tube in the probe immediately after mixing the substrate and NaOD solution together and repeatedly recording the integration curve in the region of the spectrum containing the signals selected to monitor the reaction. Slower reactions were followed by periodically recording the

spectrum of a sample thermostated in a water bath at the desired temperature. For all runs good first-order kinetics were obtained ($r > 0.99$). Kinetic runs were reproducible to ± 5% and reactions were followed to 85—90% completion. The rates of hydrolysis were determined from the disappearance of the substrate. k_{P-O} and k_{P-N} for $(MeO)_2P(O)N$⟨ (22a) were determined from k_{obs} and the known proportion of products formed by P-O and P-N bond cleavage. It was difficult to determine the rates of P-O and P-N bond cleavage accurately for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) since initial ring closure to form $(MeO)_2P(O)N$⟨ (22a) resulted in a reaction mixture which had a fairly complex ^1H n.m.r. spectrum. It was, however, possible to determine the product ratio, and thus k_{P-O}/k_{P-N} for (16a), from the integrated height of the ethylenimine hydrogen atoms as discussed in Chapter 5.2.3.

The variation of k_{P-O}/k_{P-N} with sodium deuteroxide concentration was determined for $(MeO)_2P(O)NHCH_2CH_2Cl$ (16a) and $(MeO)_2P(O)N$⟨ (22a). The substrate was introduced into an n.m.r. tube and the required amounts of NaOD solution and D_2O were added. The spectra were measured several times during the course of the reaction and k_{P-O}/k_{P-N} was determined. This ratio was constant during each kinetic run. The results have been presented in Table 15 (see Chapter 5.2.3).

7.5.3 REACTIONS WITH OTHER NUCLEOPHILES

(a) Methoxide ion

$(MeO)_2P(O)N$⟨ (22a): Equimolar amounts of substrate and sodium were dissolved in methanol-d_4 with exclusion of moisture and the mixture was allowed to stand at 25 °C for 24 hours. Three new peaks appeared in the ^1H n.m.r. spectrum. They were identified by addition of authentic material as $(MeO)_3PO$

(99), δ 3.75, d, and MeOH, δ 3.30, s, the products of P-O bond cleavage and ethylenimine δ 1.62, s, the product of P-N bond cleavage. The ratio k_{P-O}/k_{P-N} was ≤ 2.2. 20% conversion of substrate to products occurred.

$Ph_2P(O)N$△ (22c): Equimolar amounts of substrate and sodium were dissolved in methanol-d_4 with exclusion of moisture and the mixture was allowed to stand at 25 °C. A new singlet at δ 1.60 appeared in the ^1H n.m.r. spectrum. It was identified as ethylenimine by addition of an authentic sample. Complete conversion to products occurred after 70 hours (see Chapter 5.2.4, Eq.90). The product of this reaction was acidified with HCl and the white solid which precipitated was collected, washed with water, and dried. The melting point of the crystals obtained was 196 - 197 °C, identical to that of diphenylphosphinic acid (Aldrich). The experiment was repeated in methanol with removal of the solvent after 4 hours. The product obtained was dissolved in water and the organic material was extracted into chloroform. It was identified as a mixture of $Ph_2P(O)N$△ (22c) and $Ph_2P(O)OMe$ (112) by ^1H n.m.r. and by addition of authentic material, δ ($CDCl_3$) 8.27 - 7.43 (m, Ph), 3.77 (d, OMe) and 2.32 (d, $J_{H,P}$ 15 Hz, NC_2H_4).

$Ph_2P(O)OMe$ (112): was dissolved in methanol-d_4 containing an equimolar quantity of sodium. It was cleaved slowly (22 hours) in this medium yielding diphenylphosphinic acid (m.p. and mixed m.p. 196—197 °C) and 1,1,1-d_3 dimethyl ether δ (MeOH-d_4) 3.38 s.

(b) Water

The hydrolysis of substrates in water was also monitored by ^1H n.m.r. 20 - 30 mg of the substrate was dissolved in D_2O in an n.m.r. tube which was placed in a water bath at 31 °C. Spectra were determined at regular intervals at a probe temperature of 31 °C. Only $(MeO)_2P(O)N$△ (22a) underwent hydrolysis

in D_2O, k_{P-N} 2.3 x 10^{-6} s^{-1}, and the following peaks were used to identify products and follow reaction kinetics.

$(MeO)_2P(O)N$⟨ (22a): δ 3.80, d, OMe; δ 2.28, d, $J_{H,P}$ 14 Hz, PNC_2H_4

P-N cleavage products: δ 3.55, $(MeO)_2PO_2^-$; δ 2.65, s, $H_2\overset{+}{N}$⟨

Products were also identified by addition of authentic materials.

P-N bond cleavage for $(MeO)_2P(O)N$⟨ (22a) in water was a slow reaction and 12 days were required to monitor 88% conversion. During this time the ethylenimine which formed gradually polymerised, giving rise to a multiplet at δ 3.33 - 2.73[101] as well as the singlet at δ 2.65. The height of the integral of both these resonances was taken as a measure of conversion of substrate to products for the determination of k_{P-N}.

(c) Fluoride ion

Equimolar quantities of substrate and anhydrous NaF (0.38 - 0.41 *M*) were dissolved in D_2O and the reaction was followed by ^1H n.m.r. The following signals were used to identify cleavage products and monitor the reactions.

$(MeO)_2P(O)NMe_2$ (21): δ 3.68, d, OMe; δ 2.68, d, $J_{H,P}$ 10 Hz, PNMe

P-N cleavage product: δ 3.55, d, $(MeO)_2PO_2^-$; δ 2.67, s, $Me_2\overset{+}{N}H_2$

After 169 hours at 31 °C 8% conversion to products was recorded.

$(MeO)_2P(O)N$⟨ (22a): δ 3.73, d, OMe; δ 2.23, d, $J_{H,P}$ 14 Hz, PNC_2H_4

P-N cleavage product: δ 3.50, d, $(MeO)_2PO_2^-$; δ 2.58, s, $H_2\overset{+}{N}$⟨

Complete conversion to products occurred after 41 hours.

The hydrolysis of $(MeO)_2P(O)NMe_2$ (21) and $(MeO)_2P(O)N$⟨ (22a) was also carried out in water containing an equimolar quantity of $NaNO_3$. The results were identical to those obtained in pure water, *viz.* (21) underwent no hydrolysis while $t_{\frac{1}{2}}$ for P-N bond cleavage in (22a) was 85 hours.

7.6 CRYSTAL AND MOLECULAR STRUCTURE OF (16d) AND (22c)

The syntheses of $Ph_2P(O)NHCH_2CH_2Cl$ (16d) and $Ph_2P(O)N$  (22c) were described in Chapter 7.3.1. Single crystals, suitable for X-ray analyses, were obtained by recrystallisation of (16d) from CCl_4 and (22c) from acetone and pet. ether. The X-ray structure determinations were carried out by Dr. M.L. Niven of the Department of Physical Chemistry, University of Cape Town. Relevant crystal and refinement data for (16d) and (22c) are presented in Table 18.

Table 18 Crystal and refinement data for $Ph_2P(O)NHCH_2CH_2Cl$ (16d) and $Ph_2P(O)N$  (22c)

	(16d)	(22c)
Molecular formula	$C_{14}H_{15}ClNOP$	$C_{14}H_{14}NOP$
Space group	P1	Pbca
Crystal system	Triclinic	Orthorhombic
a Å	10.105(2)	11.902(4)
b Å	10.892(1)	16.556(2)
c Å	14.122(5)	12.879(1)
α	70.67(2)°	90.00(2)°
β	86.95(2)°	90.00(2)°
γ	82.27(1)°	90.00(2)°
Z	4	8
Mo-K_α radiation	λ = 0.71069 Å	λ = 0.71069 Å
Number of reflections collected	5316	2555
Number of reflections observed	2232	1285
Criterion for observed reflections	$I_{rel} > 2\sigma(I_{rel})$	$I_{rel} > 2\sigma(I_{rel})$
$R = \Sigma \lvert\lvert F_o \rvert - \lvert F_c \rvert\rvert / \Sigma \lvert F_o \rvert$	0.064	0.040
$R_w = \Sigma w^{\frac{1}{2}} \lvert\lvert F_o \rvert - \lvert F_c \rvert\rvert / \Sigma w^{\frac{1}{2}} \lvert F_o \rvert$	0.063	0.038
Weighting scheme	$(\sigma^2 F)^{-1}$	$(\sigma^2 F)^{-1}$

(16d) was solved partly by a Patterson map (location of phosphorus atoms) and partly by direct methods using a preliminary version of SHELXS-'84.[102] All non-hydrogen atoms of (22c) were located in an E-map generated by the direct-methods module of SHELXS-'84, running on default. Both structures were refined using SHELX-76.[103] In the final refinement of (16d) the P and Cl atoms were treated anisotropically with all remaining atoms isotropic. In the final refinement of (22c) all non-hydrogen atoms were assigned anisotropic thermal motion. For both structures the hydrogen atoms were included in the refinements in calculated positions.

The full crystallographic experimental data and atomic co-ordinates for this work will be published elsewhere.[104]

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REFERENCES AND NOTES

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