THE STRUCTURE AND REACTIVITY OF N-ACYL PHOSPHORIC AMIDES AND RELATED SYSTEMS

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by

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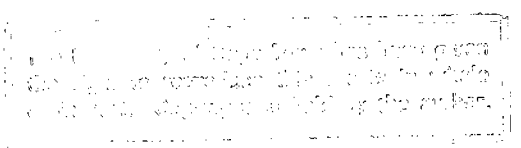

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to my parents

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Abstract

ABSTRACT

Two synthetic approaches towards the N-acyl phosphylamide system $Z_2P(O)$-NR-C(O)R' (1; Z = alkyl, O-alkyl; R = H, Me; R' = Me, Ph), from phosphylamide and carboxamide precursors are discussed. The infrared, ^1H and ^{13}C NMR spectral features of system (1), indicate predominant resonance interaction of the nitrogen non-bonding electrons with the adjacent carboxyacyl, rather than phosphacyl centre. The electron-withdrawing effect of the phosphyl substituent $Z_2P(O)$, is nonetheless substantial, thus weakening the basicity and nucleophilicity of the nitrogen atom and enhancing the electrophilicity of the carbonyl centre. The influence of the electronic distribution within the OPNCO moiety upon the structure and reactivity of (1), has been investigated.

The molecular and crystal structure of N-benzoyl dimethylphosphoramidate has revealed a planar, *cis-trans* arrangement of the OPNHCO moiety, facilitating the dimeric association of pairs of molecules via P=O•••H-N hydrogen bonding. The resulting C=O•••P^{IV} close contact is viewed as an "early stage" of face-approach nucleophilic displacement at the phosphoryl centre.

The electron impact-induced fragmentation patterns of substrates (1) have been compared with those of related amides and imides, revealing a certain degree of retention of the fragmentation characteristics of related carboxamide systems. However, a novel and prominent feature is exhibited by the molecular ions derived from (1), involving initial isomerisation to the corresponding O-phosphyl imidate, $Z_2P(O)$-O-C(NR)R', which undergoes subsequent fragmentation via C-O fission. In addition, selected tertiary substrates (1; Z = O-alkyl, R = Me) undergo thermal disproportionation to tetraalkylpyrophosphate under typical mass spectral recording conditions.

The ethylation reactions of the sodium salt of N-benzoyl dimethylphosphoramidate have been investigated as a means of probing the nucleophilicity of (1). Reaction at low temperature with triethyloxonium ion yields both phosphoryl and carbonyl oxygen-ethylated products, whereas the phase transfer-catalysed reaction with ethyl iodide at elevated temperature yields only the carbonyl oxygen-ethylated product as a pair of (E/Z) geometrical isomers. The NMR spectra and fragmentation patterns of the products are discussed.

The neutral and acid-catalysed solvolytic behaviour of (1) has been analysed and compared with that of related systems. The structural dependence of the rate of neutral P(O)-N solvolysis of (1) suggests a mechanism involving an oxyphosphorane intermediate. The ionisation behaviour of (1) in D_2O-D_2SO_4 mixtures follows the amide acidity function, with half-protonation at the carbonyl oxygen atom occurring at approximately 70% D_2SO_4. The remarkable resistance of the P(O)-N solvolysis of (1) to acid catalysis, is consistent with the exclusion of the nitrogen atom as a competitive basic centre. In contrast, the apparent susceptibility of the N-C(O) solvolysis towards acid catalysis, is in accordance with both carbonyl oxygen protonation and the significant electron-withdrawing effect of the N-phosphyl substituent, resulting in an activation of the carbonyl centre towards nucleophilic attack. Application of the Hydration Parameter Treatment to the acid-catalysed N-C(O) hydrolysis of (1b; Z = EtO, R = R' = Me), has revealed an unusually low hydration requirement of the rate-determining transition state, which is interpreted in terms of intramolecular stabilisation of the tetrahedral intermediate by the P=O group. Comparison has shown that the acidic solvolytic behaviour of (1), with respect to both the P(O)-N and N-C(O) cleavage reactions, lies between the extremes defined by the respective parent amide and symmetrical imide systems.

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Conference Proceedings

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2. The Dynamics of the Phosphoryl-Nitrogen and Nitrogen-Carbonyl Bonds in Mixed Phosphoric-Carboxylic Imides, V. Mizrahi and T.A. Modro, Third International Conference on The Mechanisms of Reactions in Solution, Canterbury, 1982.

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2. Alkylation of Ambident Ions Derived from Phosphoric-Carboxylic Imides. N-Benzoyl-O,O-Dimethyl-O-Ethyl Phosphorimidate and E/Z O-Ethyl-N(Dimethylphosphoryl)Benzimidate, V. Mizrahi, T. Hendrickse and T.A. Modro, *Can. J. Chem.*, in press.

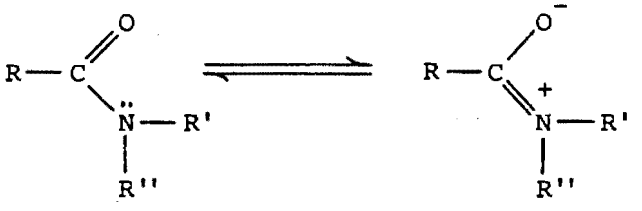
3. Phosphoric-Carboxylic Imides. I. Preparation and Fragmentation Behaviour of Dialkylphosphoryl- (and phosphinyl) Acetyl (and-Benzoyl) Imides and Related Systems, V. Mizrahi and T.A. Modro, *J. Org. Chem.*, 47, 3533 (1982).

4. Phosphoric-Carboxylic Imides. II. Solvolytic Cleavage of the Nitrogen-Carbonyl and Nitrogen-Phosphoryl Bonds, V. Mizrahi and T.A. Modro, submitted for publication to *J. Org. Chem.*

CHAPTER 1

Introduction

The important biochemical role of the carboxamide moiety, as the bridging link between individual amino acids in a polypeptide chain, has earned the carboxylic amides a place amongst the most extensively studied classes of organic compounds.[1] The interpretation and prediction of the structural and chemical properties of a carboxylic amide, are based upon an understanding of the electronic structure of the carboxamide moiety. In this regard, the influence of resonance interaction between the nitrogen non-bonding electrons and the adjacent acyl centre, is of prime importance:

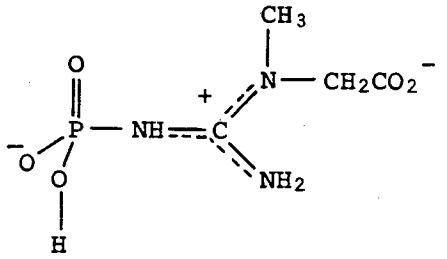


(1.1) (1.2)

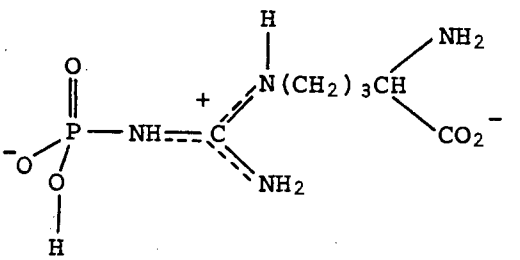
N-Acyl conjugation is best described in terms of 2p-orbital overlap between the nitrogen and carbonyl carbon atoms, rendering planarity to the nitrogen atom and partial double bond character to the carbon-nitrogen bond,[2] with a concomitant weakening of the carbonyl bond. The chemical manifestations of this type of electronic interaction, are concerned with the modification of the electron densities at the reactive nitrogen, carbon and oxygen sites. Extensive conjugation leads to a decreased availability of the nitrogen non-bonding electrons for reaction with external electrophilic reagents and, is obviously accompanied by an increase in the basicity and nucleophilicity of the carbonyl oxygen atom. In addition, a significant contribution of structure (1.2) decreases the electrophilicity of the carbonyl centre, resulting in a resistance towards nucleophilic attack and a remarkable stability of the amide linkage.

In comparison, the natural occurrence of the phosphylamide[4] moiety is much

less widespread, being limited to a small and select class of energy-rich phosphorylated guanidines, or "phosphagens", such as phosphorocreatine (1.3) and phosphoroarginine (1.4):



(1.3)

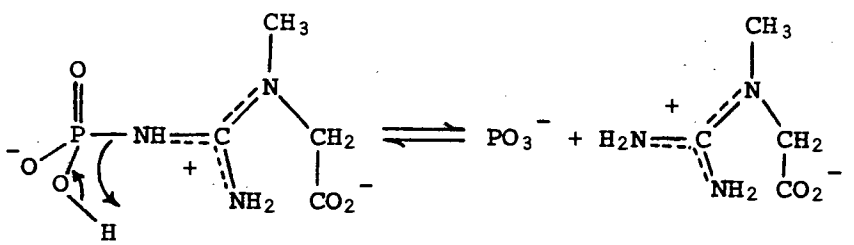


(1.4)

The vital role played by the phosphagens as biochemical phosphorylating agents, used in the regulation of the ATP concentration in living cells, is attributed to the extreme hydrolytic instability of the P(O)-N linkage under acidic conditions. Considerable interest has been expressed in elucidating the nature of the creatine kinase-catalysed phosphorylation of ADP by phosphorocreatine (PC) in muscle under severe strain (eq. 1.1):

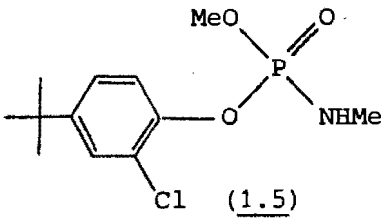
$$H^+ + ADP + PC \overset{Mg^{2+}}{\rightleftharpoons} ATP + creatine \qquad [1.1]$$

The *in vitro* solvolytic investigations,[6-8] conducted to provide a basis for understanding this *in vivo* phosphorylation process, indicate a unimolecular-type mechanism, in which initial proton transfer to the nitrogen atom precedes the collapse of the substrate to the metaphosphate and guanidinium ions (eq. 1.2):[6]

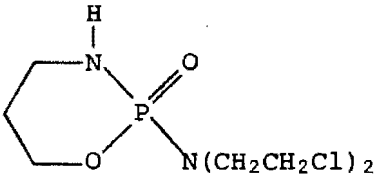


[1.2]

The potential lability of the P(O)-N linkage has been exploited in the development of pesticides,[9] such as ruelene (1.5) and, more recently, in the development of anti-cancer drugs, such as cyclophosphamide (1.6).[10]

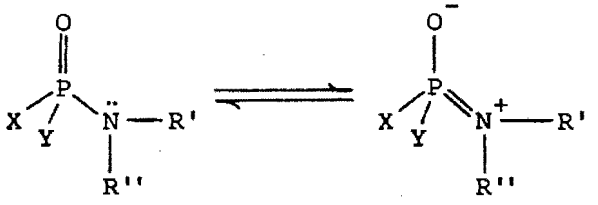


(1.5)



(1.6)

Essential to the understanding of the chemical reactivity of a phosphylamide (1.7), is a description of the nature of the resonance interaction of the nitrogen non-bonding electrons with the adjacent phosphacyl centre and hence, the relative contribution of the resonance structure (1.8).

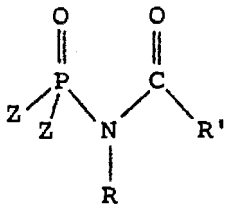


(1.7) (1.8)

The intuitive expectation of less pronounced resonance effects in the phosphylamide, as opposed to the carboxamide system, is based upon the involvement of the different 2p and 3d atomic orbitals in the former, resulting in a relatively low degree of orbital overlap. This prediction is supported by the results of the study conducted by Modro,[11] in which ^{13}C NMR spectroscopy was used to quantitatively compare the resonance and inductive effects of the phosphyl group, $Z_2P(O)$ (Z = Cl, Me, OEt, Ph, NEt_2) and the acetyl group, with respect to the non-bonding electrons of an adjacent nitrogen atom. The dual substituent parameter (dsp) approach was applied in evaluating the inductive and resonance constants (σ_I and σ_R° respectively) of the NHX substituents within a series of N-substituted anilines, Ph-NHX (X = H, $P(O)Z_2$, C(O)Me). The observed 60% decrease of σ_R° upon

N-acetylation, as opposed to the average 30% decrease caused by phosphacylation of the nitrogen atom, unambiguously demonstrates the greater effectiveness of the classical $p_{\Pi} - p_{\Pi}$ conjugative interaction in the carboxamide system, than the $p_{\Pi} - d_{\Pi}$ interaction available to the phosphylamide system.[12] The geometrical constraint applied to the nitrogen atom of (1.7), by virtue of the $p_{\Pi} - d_{\Pi}$ interaction with the adjacent phosphyl group, is therefore relatively minor, thus facilitating a shift towards pyramidality and enhancing the availability of the nitrogen non-bonding electrons for reaction with external electrophiles. In this respect, the relative ease of proton transfer to the nitrogen atom of (1.7), has been generally accepted as a critical factor in the activation of the P(O)-N bond towards nucleophilic cleavage[13] (c.f. eq. 1.2).

A direct approach towards a comparative investigation of the nature and extent of N-acyl interactions, is offered by the N-acyl phosphylamide system (1), which represents an incorporation of two different amide moieties into the same molecular framework.



(1)

The Π-electronic distribution within the OPNCO moiety of the "mixed imide" (1), has a strong influence upon the relative basicities and nucleophilicities of the phosphyl and carbonyl oxygen and mixed imidic nitrogen atoms, as well as the relative electrophilicities of the phosphyl and carbonyl centres. The competitive resonance interaction of the nitrogen non-bonding electrons with the adjacent phosphyl and carbonyl centres, thus

constitutes a major factor in defining the chemical behaviour of (1).

The available information concerning the general properties of the acyclic N-acyl phosphylamide system (1), is both scarce and non-systematic, being essentially limited to reports describing synthetic procedures for the preparation of N-acyl phosphoramidates (1; Z = RO, ArO),[14-23] their potential pesticidal value[21] and the mechanistic details of the phosphorylation reactions of N-benzoyl phosphoramidic acid and its conjugate bases.[24,25] In light of the potential chemical insight offered by the mixed imide system (1) into the comparative properties of the parent amide systems, a systematic study of the structure and reactivity of selected members of this class of compounds was undertaken. The representative substrates (1a-g) were specifically chosen, with the aim of investigating the response of the chemical behaviour of the mixed imide system, to structural variation at the phosphorus, nitrogen and carbonyl carbon atoms.

$(MeO)_2P(O)$-NH-COPh

(1a)

$(EtO)_2P(O)$-NH-COPh

(1b)

$(MeO)_2P(O)$-NMe-COMe

(1c)

$(EtO)_2P(O)$-NMe-COMe

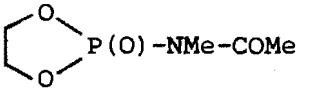
(1d)

$(EtO)_2P(O)$-NMe-COPh

(1e)

$Et_2P(O)$-NMe-COPh

(1f)



(1g)

Attention was firstly focussed upon elucidating the relationships existing between molecular structure, electronic structure and chemical reactivity

of the mixed imide system (1), with particular reference to its electron impact fragmentation, nucleophilic and solvolytic characteristics, and secondly, classifying the mixed imide system with respect to its parent amide and symmetrical phosphoric and carboxylic imide systems, by means of the relevant comparative investigations.

CHAPTER 2

The Synthesis of N-Acyl Phosphylamides

2.1 INTRODUCTION

Aroyl phosphoramidic acids and their mono- and diester derivatives, were first prepared by Titherley and Worrall[14] in 1909, according to the following scheme:

$$PCl_5 + ArCONH_2 \xrightarrow{\text{benzene}} ArCONH\text{-}P(O)Cl_2$$

$$\Big\downarrow \; SOH \quad (S = H, \text{alkyl})$$

$$ArCO\text{-}NH\text{-}P(O)(OS)_2$$

In anticipation of their potential pesticidal activity, a revival of interest in these compounds followed some fifty years later, leading to the development of new synthetic approaches from a variety of organophosphorus precursors. The most popular and well documented route to the secondary N-acyl phosphoramidates, is via alcoholysis of the readily accessible N-acyl trichlorophosphorimidates, as described by Kirsanov and Makitra.[15] This method was successfully applied to the synthesis of the secondary N-benzoyl substrates (1a,b) (eq. 2.1):

$$PhCONH_2 + PCl_5 \longrightarrow PhCO\text{-}N{=}PCl_3 + 2HCl$$

$$\Big\downarrow \; \text{(i) } 3RONa/ROH \; (R = Me, Et) \quad \text{(ii) } H^+ \qquad [2.1]$$

$$R_2O + 3NaCl + PhCO\text{-}NH\text{-}P(O)(OR)_2$$

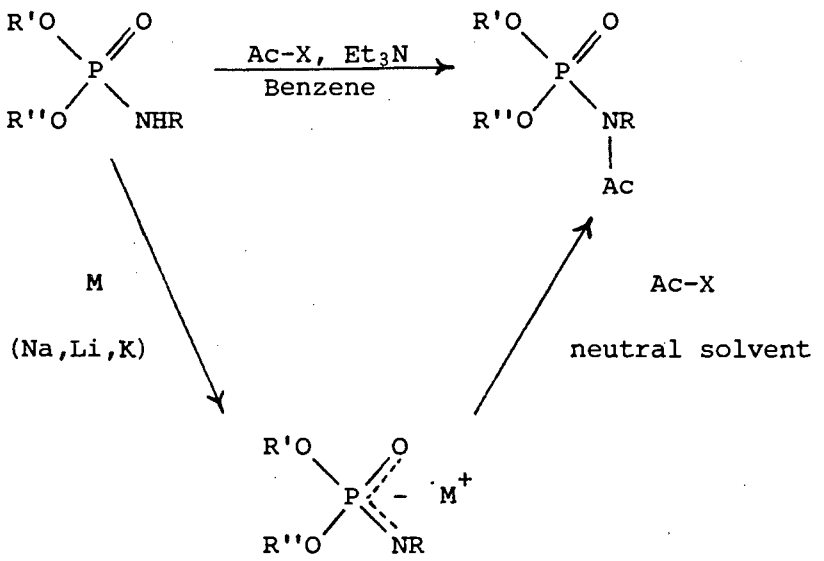
(1a,b)

The secondary derivatives can also be readily prepared by the acidolysis of precursors such as N-acyl trialkylphosphorimidates[16-18,20] and N-phosphoryl imidates.[18,19] In contrast, the available information concerning the synthesis of tertiary N-acyl phosphoramidates is scarce, and the reported

products are insufficiently characterised. Kabachnik *et al.*[20] have reported the formation of N-acetyl N-phenyl diethylphosphoramidate by the acetylation of N-phenyl triethylphosphorimidate with acetyl chloride at elevated temperature (eq. 2.2):

$$(EtO)_3P{=}N\text{-}Ph \xrightarrow[\text{ligroine}]{MeCOCl,\ 70°C} (EtO)_2P(O)\underset{\displaystyle COMe}{\underset{|}{N}}Ph \qquad [2.2]$$

The reports by Perkow,[21] Alimov *et al.*[22] and Matrosov *et al.*[23] claim facile N-acylation of a wide range of substituted phosphoramidates under basic conditions (eq. 2.3):



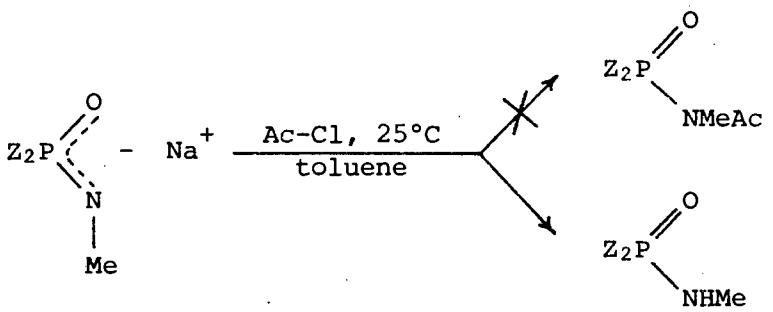
[2.3]

In view of the literature reports, the base-catalysed acylation of the readily accessible N-substituted phosphylamide precursors $Z_2P(O)NHR$ (2.1), appeared to be the most attractive route to the tertiary N-acyl phosphylamidates.

2.2 THE N-ACYLATION OF PHOSPHYLAMIDES

2.2.1 BASIC CONDITIONS

Contrary to expectation based on literature reports,[21-23,26] the reactions of the sodium salts of N-methyl diphenylphosphinamidate and N-methyl diethylphosphoramidate with acetyl chloride in toluene, failed to yield the desired N-acetylated products. A possible explanation of the observed quantitative regeneration of unreacted amide, is the behaviour of the phosphylamide anions as bases, rather than nucleophiles, towards acetyl chloride. The abstraction of an acidic hydrogen from acetyl chloride, would result in the regeneration of the amide and the expulsion of ketene (eq. 2.4):



[2.4]

(Z = Ph, EtO)

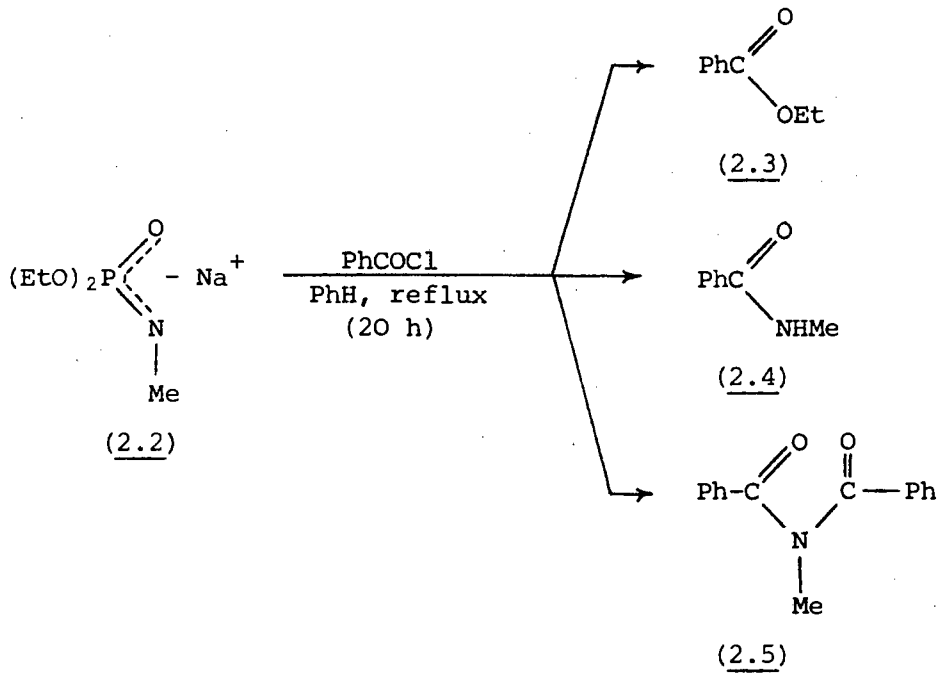
+ CH_2CO + NaCl

In an attempt to eliminate this alternative reaction pathway, the acylating agent was replaced by one bearing no acidic hydrogens, namely benzoyl chloride.

The reaction of the sodium salt of $(EtO)_2PONHMe$ with benzoyl chloride in benzene is negligibly slow at ambient temperature. The reaction mixture was therefore heated with periodic monitoring by thin-layer chromatography (TLC). Complete disappearance of the substrates was apparent after 20 h under reflux. However, the complexity of the product mixture (as illustrated by TLC) and the absence of a low-field N-methyl doublet in its ^1H NMR spectrum (see Chapter 2.3), indicated that a simple condensation reaction, to yield the desired N-benzoyl mixed imide, had not occurred. The product mixture

obtained after aqueous work-up was separated into its components by column chromatography and the products identified by a combination of spectroscopic techniques. As illustrated in Scheme 2.1, none of the products isolated from the mixture is phosphorus-containing.

Scheme 2.1

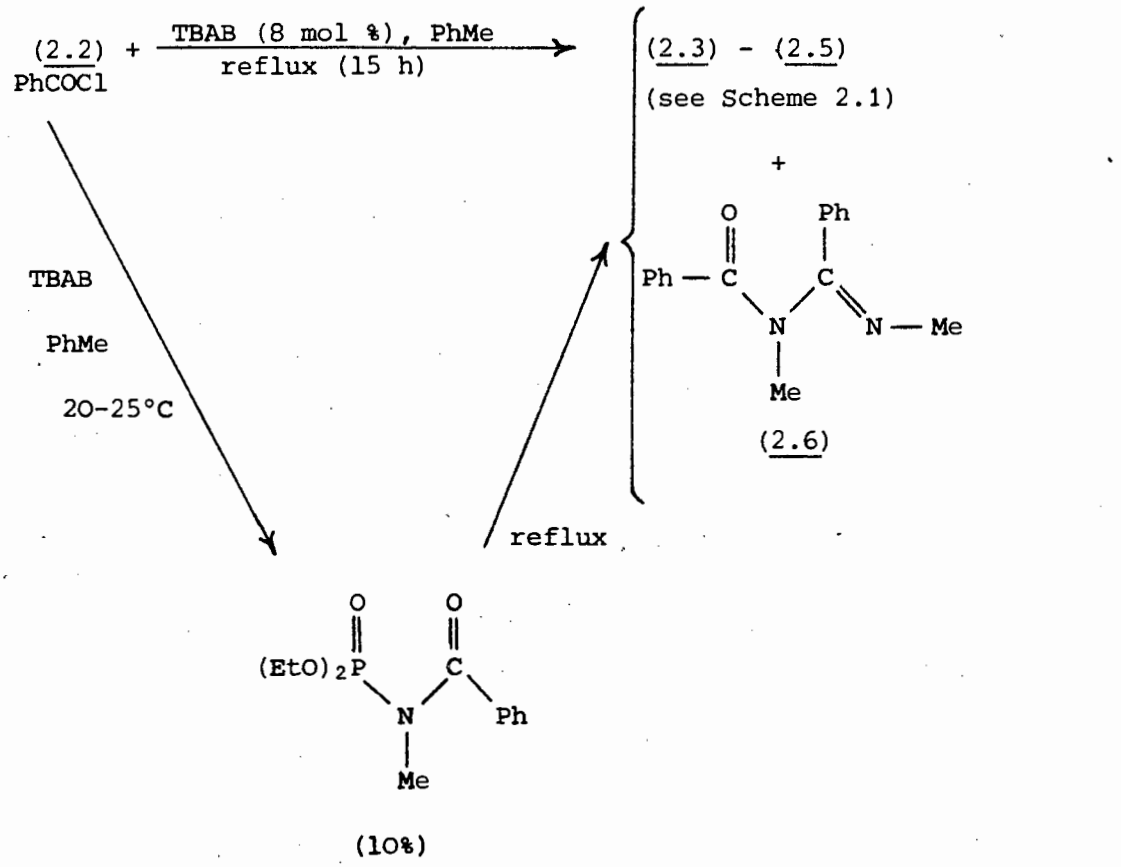


Since it is evident that an elevated temperature favours formation of the benzoyl derivatives (2.3) - (2.5) over the mixed imide, attempts were made to enhance the nucleophilicity of the phosphoramide anion, to enable the reaction to proceed at a lower temperature. Since significant reactivity enhancement of bulky, charge-buried, "soft" nucleophiles, can be achieved under conditions of phase transfer catalysis,[27,28] the reaction of the phosphoramide anion (2.2) with benzoyl chloride in toluene, was carried out in the presence of a catalytic amount (8 mol %) of tetra-n-butylammonium bromide (TBAB). The reaction at ambient temperature resulted in the formation of a new product, characterised by the appearance of a low-field N-methyl doublet (δ 3.15, J(PNCH) 8 Hz) in the ^{1}H NMR spectrum of the product mixture, indicative of mixed imide formation.[29] However, since the percentage

conversion of (2.2) to the mixed imide is only 10% after 5 days stirring at 20 - 22°C, the reaction was repeated at an elevated temperature.

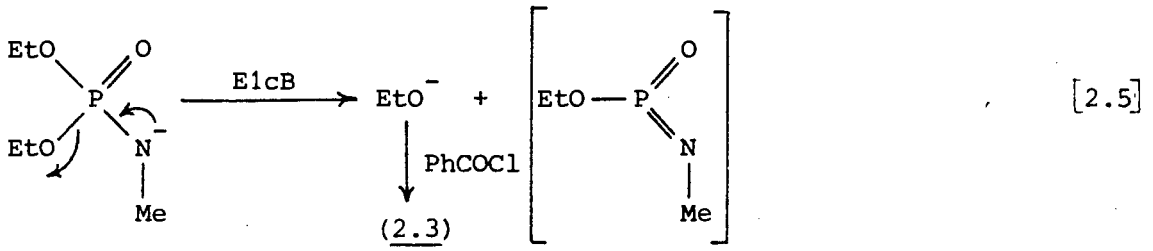
The progress of the reaction conducted in toluene under reflux, was monitored by TLC and ^{1}H NMR spectroscopy. After the initial formation of approximately 10% mixed imide, the appearance of four new products, accompanied by disappearance of the substrates and mixed imide, is observed. After 15 h under reflux, the ^{1}H NMR spectrum of the product mixture indicated total disappearance of the mixed imide and the substrates. Therefore, although a small quantity of mixed imide is initially formed, it does not survive in the medium. The product mixture obtained after filtration and evaporation was separated into its components by column chromatography and the reaction products were spectroscopically identified (Scheme 2.2).

Scheme 2.2



The final product mixtures obtained under the conditions outlined in Schemes 2.1 and 2.2, are very similar, except for the appearance of the benzamidine derivative (2.6) in the phase transfer-catalysed reaction.

The formation of ethyl benzoate (2.3) under the given reaction conditions, is best explained in terms of unimolecular expulsion of ethoxide ion from the phosphoramidate conjugate base and subsequent trapping by benzoyl chloride to yield (2.3) (eq. 2.5):

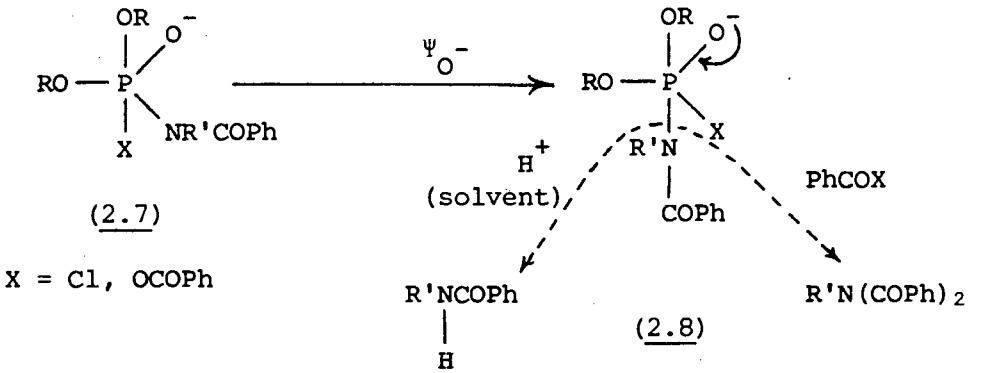


[2.5]

This type of mechanism (E1cB) has been proposed to operate in the base-catalysed solvolysis of certain phosphoramidic chlorides and esters, in order to explain the considerable rate differences observed between substrates bearing an abstractable hydrogen at nitrogen, and those in which the nitrogen is fully substituted.[30] Since no effort was made to isolate the phosphorus-containing products of the reaction mixture, the fate of the reactive meta-phosphorimidate product is, as yet, unknown. However, this product would probably polymerise or react with traces of moisture, to give acidic products which are insoluble in organic solvents. The phosphorus-containing product would thus be removed from the toluene solution, thus accounting for the absence of organophosphorus products in the final product mixture (Scheme 2.2).

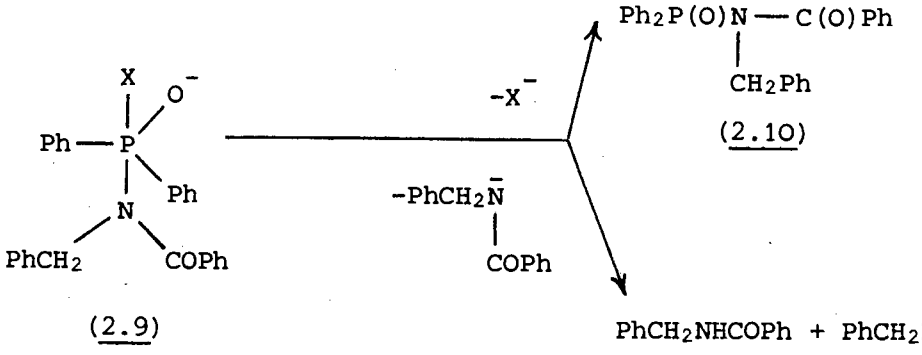
The remaining three products (2.4), (2.5) and (2.6), all contain the common carboxamide moiety PhCONMe, which apparently arises from an"N-methyl group transfer" from the diethylphosphoryl to the benzoyl group. It has been found that a carboxylic acid precursor can be converted into a corresponding carboxamide derivative by heating, in the presence of base, with a variety

of pentacovalent phosphorus amides such as phosphoric amides[31,32] and N-aroyl phosphorimidic triamides.[33] However, no mechanistic proposals for the migration of the nitrogen-containing moiety from phosphorus to carbon, were made in these literature reports. In the most recent and relevant study concerning the nitrogen group transfer phenomenon, Edmundson and Moran[26] report the formation of N-substituted benzamides and dibenzimides (c.f. (2.4) and (2.5)) in the reaction of a variety of phosphylamidate anions with benzoylating agents (benzoyl chloride, benzoic anhydride). The mechanism of nitrogen group transfer is discussed in terms of pseudorotation of the initially formed pentacoordinate intermediate (2.7) to (2.8), followed by apical departure of the carboxamide moiety via either of the pathways illustrated in eq. 2.6:



[2.6]

This mechanism is, in principle, feasible, despite the lack of supporting evidence; however, it fails to account for the nitrogen group transfer observed from the phosphinic (rather than phosphoric) amide precursor $Ph_2P(O)\bar{N}CH_2Ph$,[26] in which the weak apicophilicity of the phenyl ligands at phosphorus, precludes the formation of the analogues of (2.7) and (2.8). The only possible P^V intermediate that could be formed in this case, is (2.9), from which either X or the acylated nitrogen could depart (eq. 2.7):

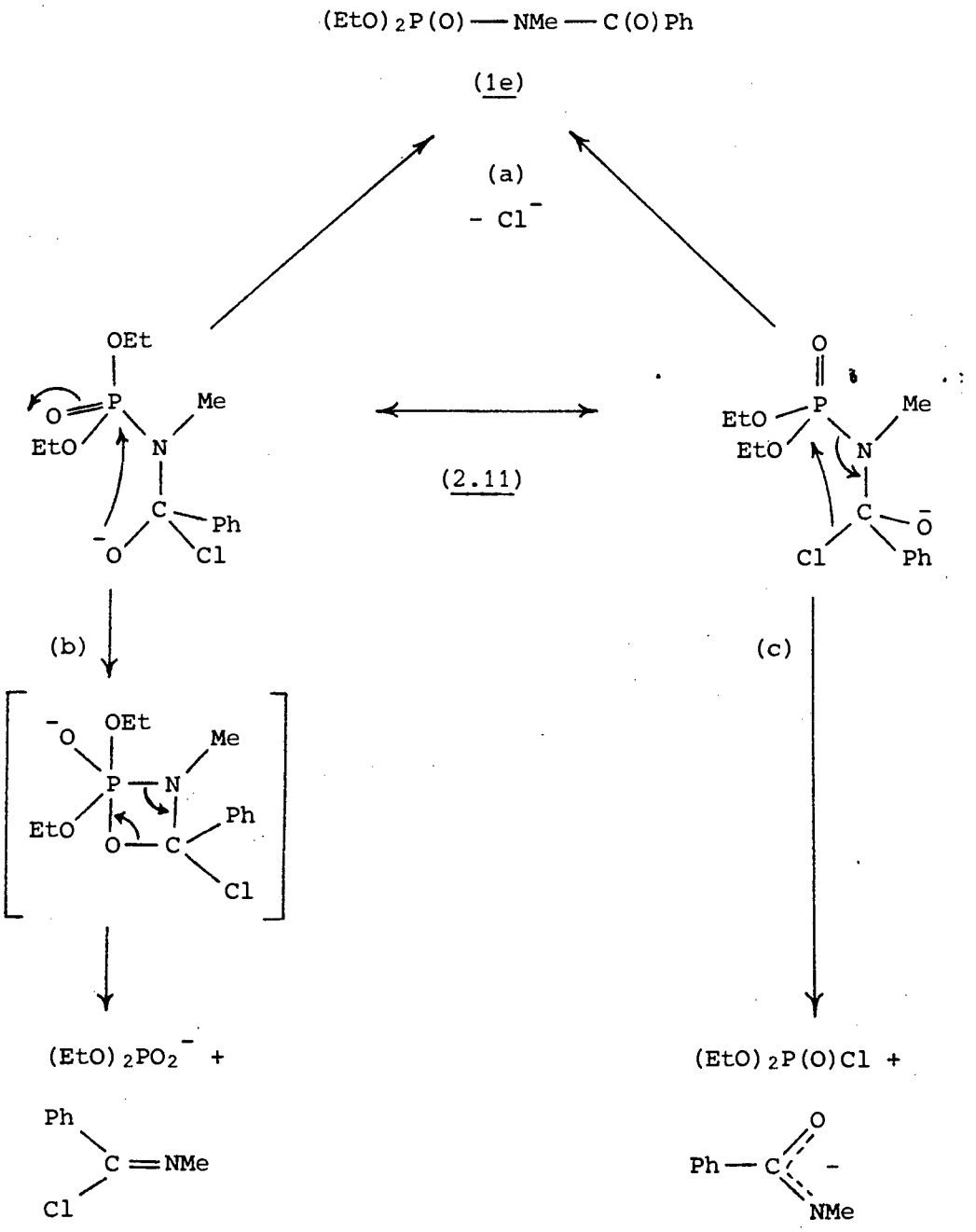


[2.7]

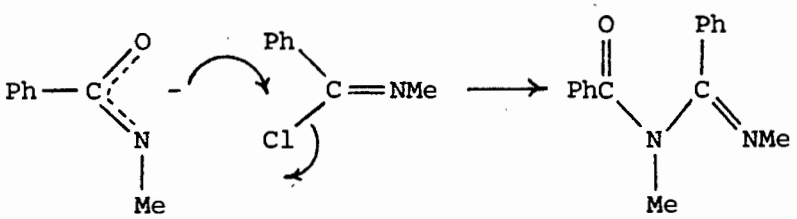
However, no mention was made of the possibility of formation of the mixed imide (2.10). It is also of interest to note that in focussing their attention on the nitrogen transfer reaction, the authors fail to comment on the participation of the unimolecular expulsion of RO^- from $(RO)_2PO\bar{N}R'$ (R = Et, Ph), which would result in the formation of ethyl or phenyl benzoate (c.f. (2.3)), as an alternative reaction pathway available to this system.[34]

Reaction of the phosphoramide anion (2.2) with benzoyl chloride via nitrogen attack, results in the formation of a tetrahedral intermediate (2.11). Collapse of (2.11) by loss of chloride ion is evident by the formation of a certain quantity, albeit small, of mixed imide (1e) at ambient temperature (Scheme 2.3, pathway a). However, the proximity of the nucleophilic oxyanion and chlorine substituents at the tetrahedral carbon atom of (2.11) to the phosphoryl centre, offers the intermediate two additional decomposition pathways, as illustrated in Scheme 2.3 (pathways b, c).

Scheme 2.3 Decomposition of the tetrahedral intermediate (2.11).



Wadsworth and Emmons[35] have found that dialkylphosphoramidate anions react smoothly with a variety of carbonyl compounds such as aldehydes, ketenes and isocyanates to yield imines, ketenimines and carbodiimides respectively, via a mechanism which is analogous to that proposed for the Wittig-Horner synthesis of olefins, from phosphonate carbanions and carbonyl compounds.[36] Formation of N-methylbenzimidoyl chloride via pathway b, Scheme 2.3, is thus an extension of the Wadsworth-Emmons reaction. However, once this reactive species is formed, it reacts with the carboxamide species generated via pathway c, to yield N-benzoyl-N,N'-dimethylbenzamidine (2.6) (eq. 2.8):

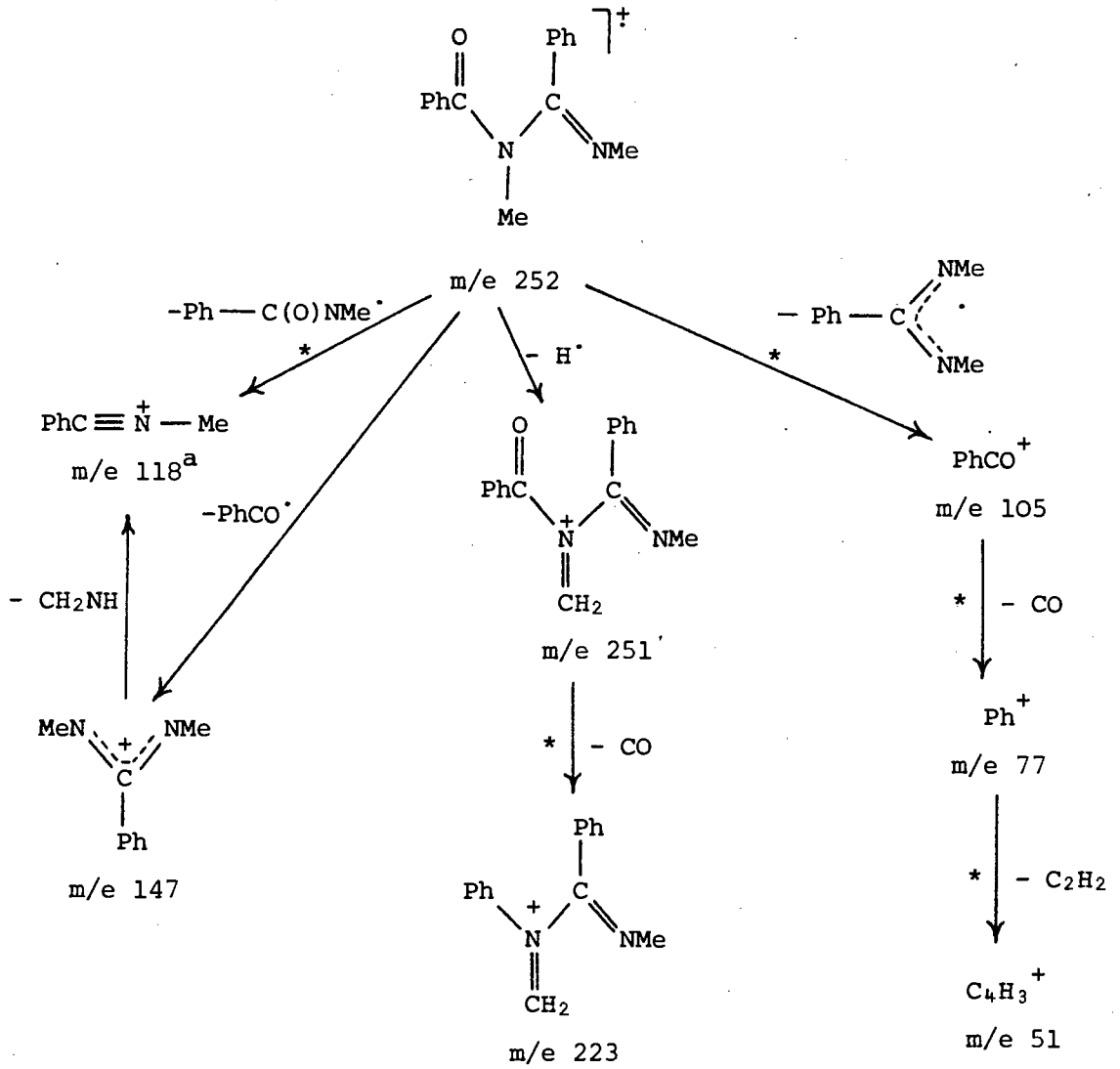


[2.8]

(2.6)

The structure of (2.6) was determined by a combination of spectroscopic techniques. The existence of two different N-methyl groups was inferred from the ^{1}H NMR spectrum (δ3.15 and δ3.25). The IR spectrum revealed the presence of both C=O and C=N groups ($\nu_{C=O}$ 1658 cm^{-1}, $\nu_{C=N}$ 1637 cm^{-1}) and the appearance of N-methylbenzonitrilium ion as the base peak in the mass spectrum, confirmed the benzamidine structure. The proposed electron impact fragmentation pattern of (2.6), is given in Scheme 2.4.

Scheme 2.4 Fragmentation pattern of (2.6).



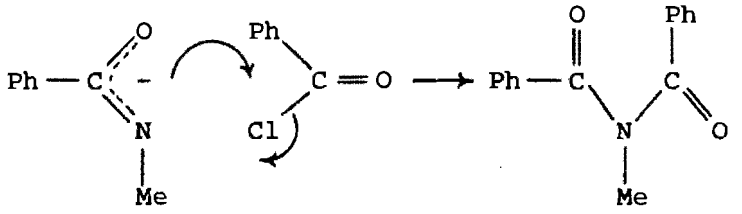
[a]Base peak

*Metastable

The formation of (2.6), as opposed to its symmetrical imidic acid anhydride isomer $(PhCNMe)_2O$, suggests that the ambident carboxamide anion reacts exclusively via the nitrogen atom.

Decomposition of (2.11) via pathway c leads to the formation of the carboxamide anion $[PhCONMe]^-$, which is a precursor of the three products (2.4) - (2.6): exposure of the anion to moisture yields the derivative (2.4), reaction with benzoyl chloride accounts for the formation of the major product (2.5) (eq. 2.9)

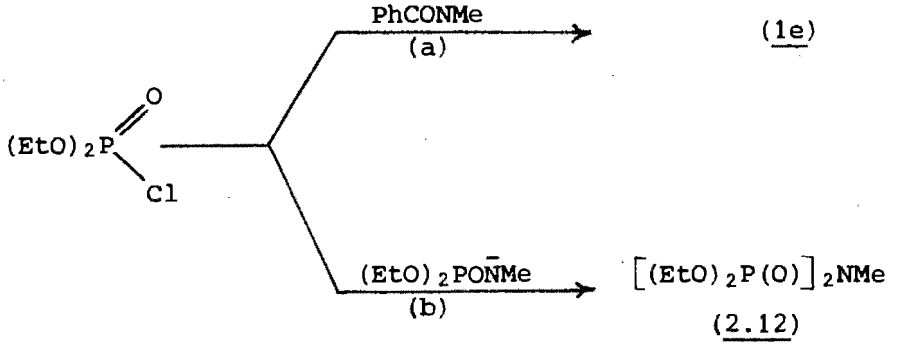
and formation of (2.6) occurs as discussed above (eq. 2.8).



[2.9]

(2.5)

The positive identification of (1e) provides evidence supporting decomposition of (2.11) via pathway a (Scheme 2.3). Similarly, the isolation and characterisation of the minor product (2.6), (5%) constitutes direct evidence in support of the proposed reaction via pathway b. However, the proposed mechanism of formation of the carboxamide anion by P—N cleavage of (2.11) via pathway c, remains speculative, since diethyl phosphorochloridate was not isolated from the reaction mixture. The presence of this highly electrophilic species in a reaction medium rich in nucleophiles, such as the phosphoramide and carboxamide anions, is expected to introduce the possibility of participation of additional competitive side reactions (eq. 2.10):



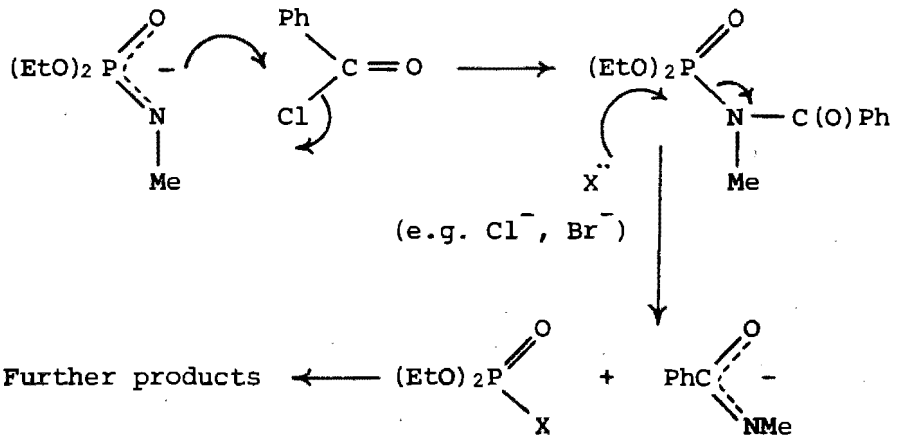
[2.10]

(2.12)

Independent experiments have shown that the chlorophosphate indeed reacts as indicated in eq. 2.10. Although reaction via pathway a (eq. 2.10) merely provides an alternative route for mixed imide formation, reaction via pathway b leads to the formation of a new product (2.12), which is characterised by a distinctive N-methyl triplet (δ 2.96, J(PNCH) 9.5 Hz) in the ^{1}H NMR

spectrum[37] and would thus be readily identifiable. In addition, the independent experiment also revealed the formation of triethyl phosphate in this reaction, by the trapping of expelled EtO^- by the chlorophosphate (c.f. eq. 2.5). Preliminary investigations have revealed that both (2.12) and $(EtO)_3PO$ are sufficiently stable to survive the reaction conditions given in Scheme 2.3. Their absence therefore argues against the participation of the side reaction given by eq. 2.10, pathway b. This, in turn, may be due to either, a greater reactivity of $(EtO)_2P(O)Cl$ towards the carboxamide rather than phosphoramide anion (predominance of pathway a), or a lack of accumulation of the chlorophosphate in the reaction medium.[38]

The observation that (1e) does not survive in the reaction medium, but rather acts as a transient species, contrasts the previous, unsubstantiated proposal of mixed imide stability under such conditions.[26] This observation therefore suggests the possibility of mixed imide intermediacy in the nitrogen group transfer reaction from phosphorus to carbon. Subsequent phosphoryl-nitrogen cleavage of (1e) requires the approach of a nucleophile X towards the phosphoryl centre, as illustrated in eq. 2.11:



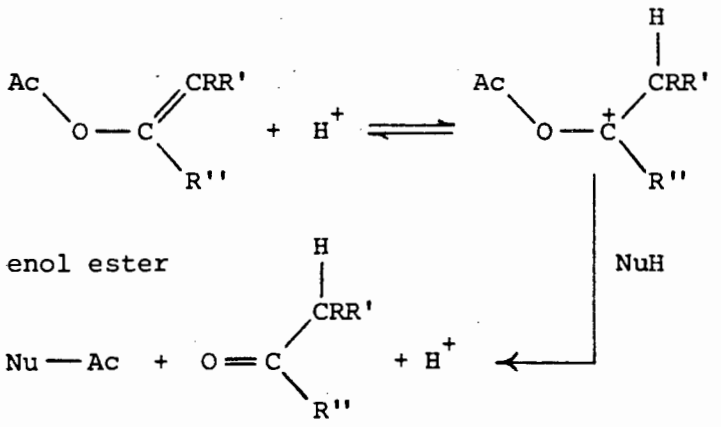
[2.11]

Owing to the complexity of the product mixture, the nature of X is, as yet, unknown. The feasibility of eq. 2.11 as a means of explaining carboxamide formation, is currently under investigation in this laboratory.

The reaction of N-substituted phosphylamides with acylating agents under basic conditions, is thus an unsatisfactory means of preparing tertiary mixed imides and leads instead, to the formation of a diverse range of carboxyacyl derivatives.

2.2.2 ACIDIC CONDITIONS

Enol esters have proved to be extremely effective acylating agents in the presence of an acid catalyst, as illustrated in eq. 2.12:



[2.12]

(Ac = acyl, Nu = nucleophile).

The high reactivity of a protonated enol ester facilitates the acylation of very weakly nucleophilic substrates such as amides, thereby affording a convenient route to di- and triacylamines.[40] The feasibility of N-acetylation of a variety of secondary phosphylamidate substrates (2.1 a-d), with isopropenyl acetate (IPA; R = R' = H, R'' = Me), in the presence of an acid catalyst, was thus investigated as a means of preparing tertiary N-acetyl phosphylamidate derivatives. Following Hagemeyer's recommendation, the acid catalyst initially used was 96% sulfuric acid.[40]

$Z_2P(O)NHR$ (2.1)

a, Z = EtO, R = Me

b, Z = MeO, R = Me

c, Z = Et, R = Me

d, Z = MeO, R = Ph

In a typical experiment, the amide (2.1) was heated in toluene with a twenty-fold excess of acetylating agent in the presence of 8 - 10 mol % H_2SO_4. The progress of the reaction was monitored by TLC and ^1H NMR spectroscopy with prior removal of all volatile materials.

Approximately 70% N-acetylation of (2.1a) is achieved after 5 h under reflux, as indicated by the presence of a low-field N-methyl doublet (δ 3.04, J(PNCH) 7.5 Hz) and acetyl singlet (δ 2.39) in the ^1H NMR spectrum of the product mixture.[29] However, prolonged heating under reflux results in the gradual disappearance of the mixed imide and the simultaneous appearance of two new singlet absorptions at δ 2.42 and δ 3.22, of integration ratio 2:1. These peaks were identified as the acetyl and N-methyl absorptions of N-methyldiacetimide (2.14a), by spiking with a genuine, independently synthesised sample.

The behaviour of the amide (2.1b) under the same conditions, is similar, but less satisfactory in terms of mixed imide formation, with a maximal relative concentration of 30% attained after a 4 h period. The product mixture was found to be contaminated at all stages of the reaction with both N-methylacetamide (2.13a) and its N-acetylated derivative (2.14a). Prolonged reaction leads to the disappearance of both the mixed imide and (2.13a) and exclusive formation of the diacetimide (2.14a).

MeC(O)-NHR		$(MeCO)_2NR$	
(2.13)	a, R = Me	(2.14)	a, R = Me
	b, R = Ph		b, R = Ph

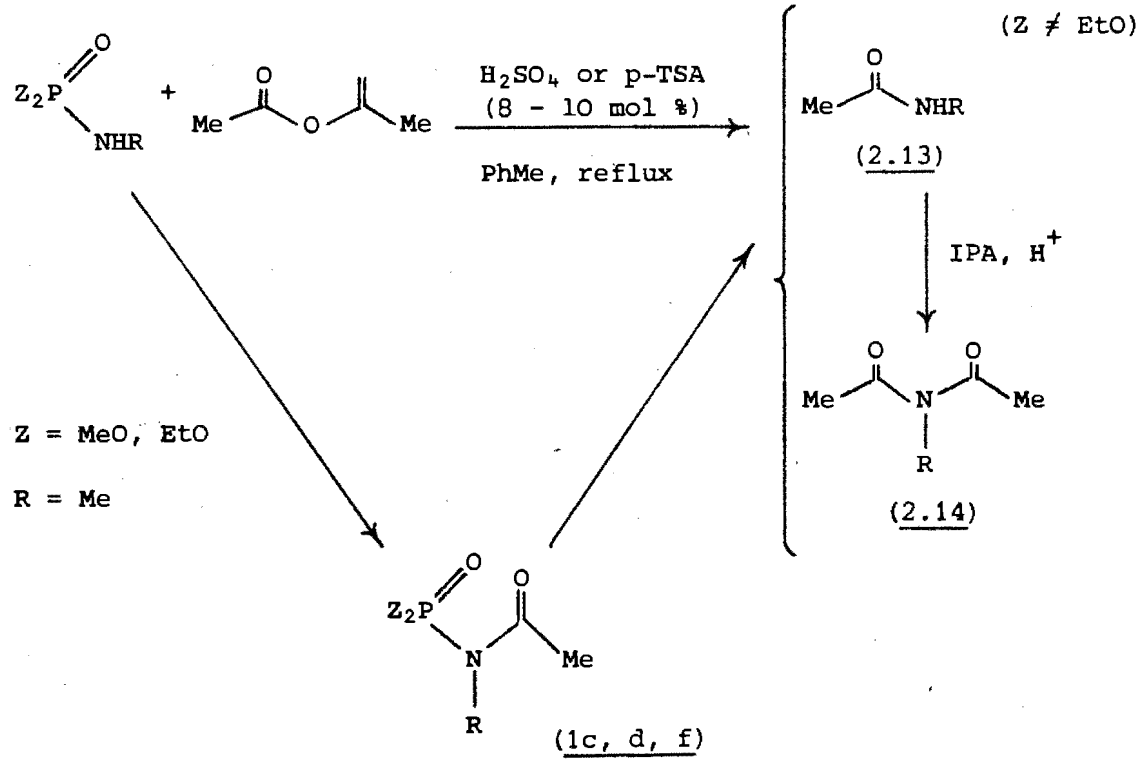
In contrast, reaction of the phosphinamide (2.1c) under identical reaction conditions, results in the exclusive formation of (2.13a), with no trace of the corresponding mixed imide (1f) evident at any stage of the reaction. The carboxamide (2.13a) is gradually acetylated in the reaction medium to yield (2.14a). Reaction of the anilide (2.1d) proceeds with the appearance

of two new absorptions in the ^1H NMR spectrum (δ 2.18, δ 2.27) which were identified as the acetyl absorptions of acetanilide (2.13b) and N-phenyl-diacetimide (2.14b), respectively.

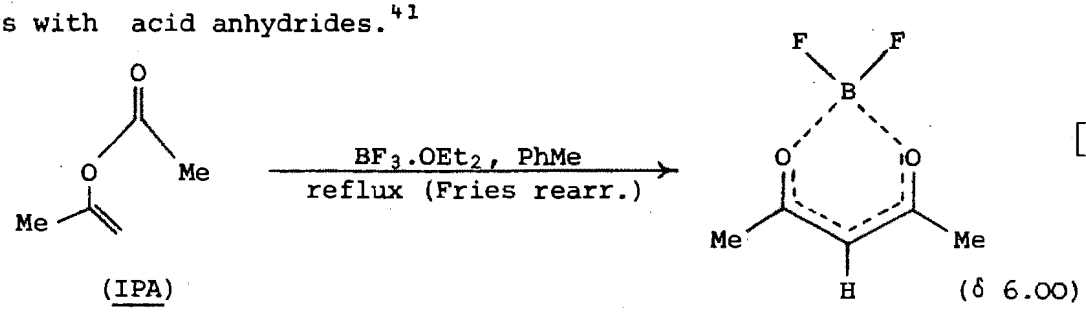
The formation of the carboxamide derivatives (2.13) and (2.14), involves a "nitrogen group transfer" process analogous to that observed under basic conditions and necessarily requires phosphoryl-nitrogen cleavage of the phosphylamidate precursors (2.1) and, where applicable, their N-acetyl derivatives. Owing to the extreme susceptibility of the P(O)-N bond to acid-catalysed solvolysis, the H_2SO_4 catalyst was replaced by anhydrous p-toluene sulfonic acid (p-TSA), with the aim of eliminating the possibility of phosphylamide hydrolysis in the reaction medium. However, although this change slows down the overall reactions, carboxamide formation is found to persist (Scheme 2.5).

In a second attempt to eliminate the nitrogen group transfer process, the protic acids were replaced by a Lewis acid, namely boron trifluoride. The reaction of (2.1b) with excess IPA in toluene under reflux in the presence of

Scheme 2.5



80 mol % $BF_3.OEt_2$, was found to parallel those catalysed by the protic acids (Scheme 2.4), with smooth conversion to the carboxamide derivatives (2.13) and (2.14). This reaction is, however, complicated by a Lewis acid-catalysed Fries rearrangement of the enol ester, IPA, to acetylacetone, which reacts with BF_3 to yield the complex (2.15) (eq. 2.13). Similar boron difluoride complexes have been previously isolated as intermediates in the preparation of β-diketones via the BF_3-catalysed acylation of enol esters with acid anhydrides.[41]



(IPA) [2.13]

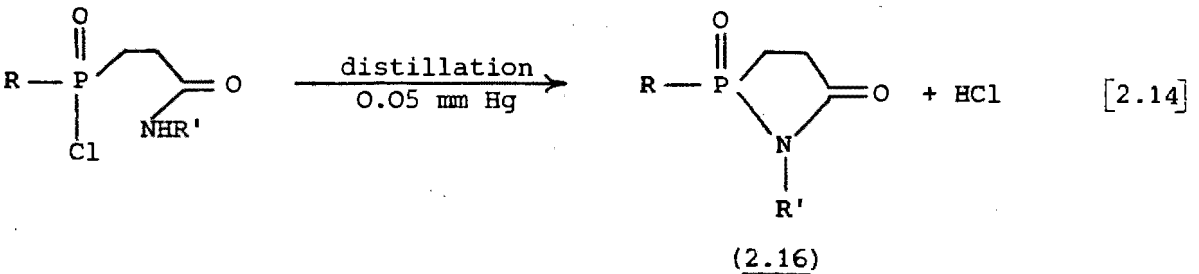
(2.15)

It is therefore clear that the general method for N-acylation of carboxamides cannot be satisfactorily applied to their phosphylamide analogues, owing to the strong tendency towards carboxamide formation via nitrogen group transfer from phosphorus to carbon. In this regard, the similarity in outcome of the acylation reactions conducted under both basic and acidic conditions, is of mechanistic significance. It has been found that the independently synthesised mixed imides (1d,f) (see Chapter 2.3) react with IPA under acidic conditions to yield the carboxamide derivatives (2.13a, 2.14a), providing evidence in support of mixed imide intermediacy in the nitrogen group transfer process. The acidic medium is however, deficient in nucleophiles capable of effecting P(O)-N cleavage of the mixed imide intermediate, and since no phosphorus-containing products were isolated, the mechanism of the second step of the nitrogen group transfer process, remains unclear. Despite mechanistic uncertainties, the acylation studies discussed above, have indicated an inherent lability of the P(O)-N rather than N-C(O) linkage of

the mixed imide system, with cleavage resulting in the formation of a resonance-stabilised, thermodynamically favoured carboxamide product.

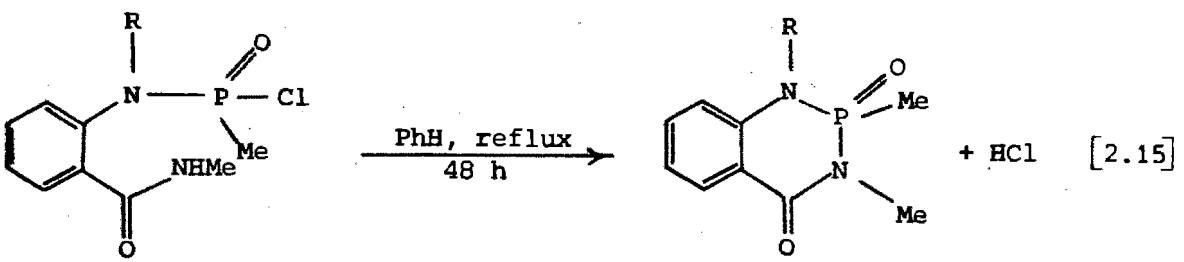
2.3 THE N-PHOSPHYLATION OF CARBOXAMIDES

The reaction of a carboxamide with a phosphylating agent, is potentially complicated by the ambident nature of the nucleophile, which enables the formation of two products, arising from kinetic and thermodynamic control, respectively. The orientation of a given reaction naturally depends upon the reaction conditions and the nature of both the reactant and the substrate. Nucleophilic displacement by a carboxamide nitrogen at a phosphacyl halide has been observed under neutral conditions, in systems in which the resulting P-N bond formation effects cyclisation. Pudovik *et al.*[42] have reported the formation of substituted 1,2-oxaphospholan-5-one-2-oxides (2.16) by vacuum distillation of the corresponding acyclic precursors (eq. 2.14) and Coppola[43] has similarly observed the formation of the substituted 1,3,2-benzodiaza-phosphorin (2.17) by intramolecular nucleophilic substitution of the acyclic precursor, in the absence of a base (eq. 2.15).



[2.14]

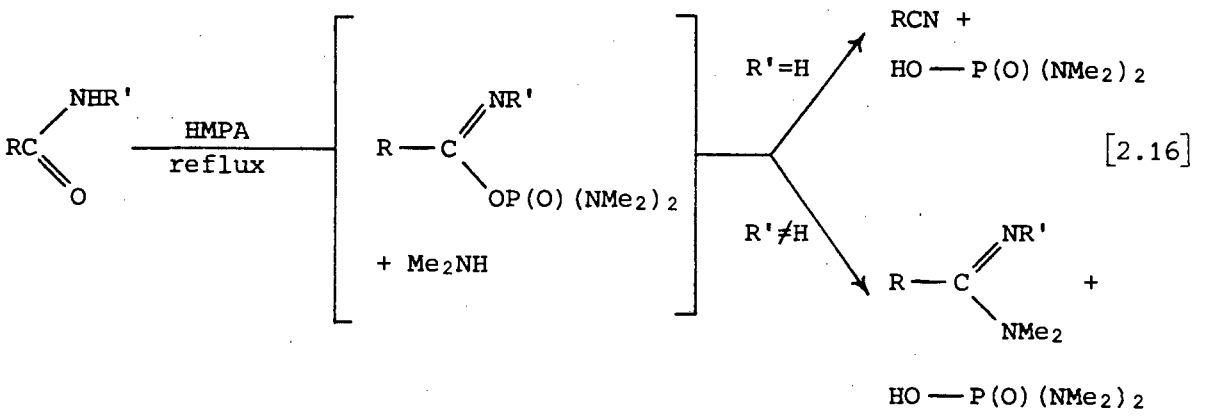
(2.16)



[2.15]

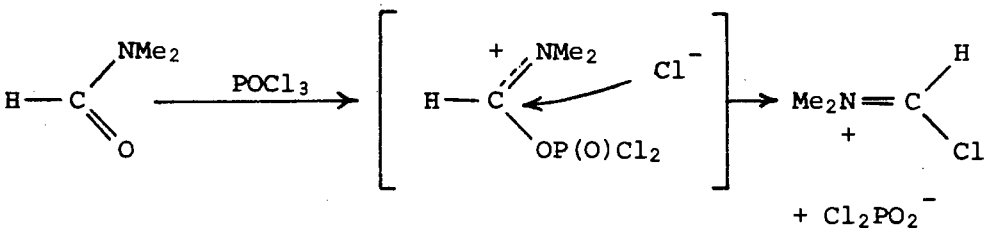
(2.17)

In contrast, intermolecular phosphylation reactions under neutral conditions, generally proceed via carboxamide oxygen attack to yield highly reactive O-phosphyl imidate products, which may undergo subsequent changes, as illustrated by the reaction of primary and secondary carboxamides with hexamethyl phosphortriamide (HMPA) to yield nitriles and amidines respectively (eq. 2.16):[44]



[2.16]

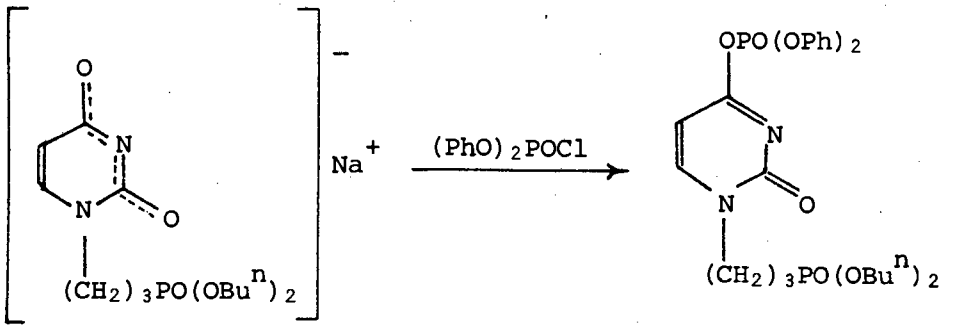
Tertiary carboxamides are capable of undergoing an analogous reaction, as indicated by the first step of the Vilsmeyer reaction,[45] involving the O-phosphylation of N,N-dimethyl formamide with phosphorus oxychloride to yield the intermediate (2.18) which reacts to produce an active formyl electrophile, as illustrated in eq. 2.17:



[2.17]

(2.18)

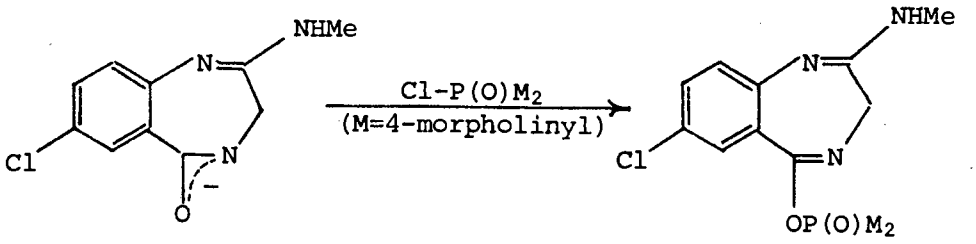
The phosphylation of less reactive carboxamides can be achieved by nucleophilic enhancement under basic conditions. Reznik *et al.*[46] have reported the exclusive O-phosphorylation of the uracil sodium salt (2.19) (eq. 2.18):



(2.19)

[2.18]

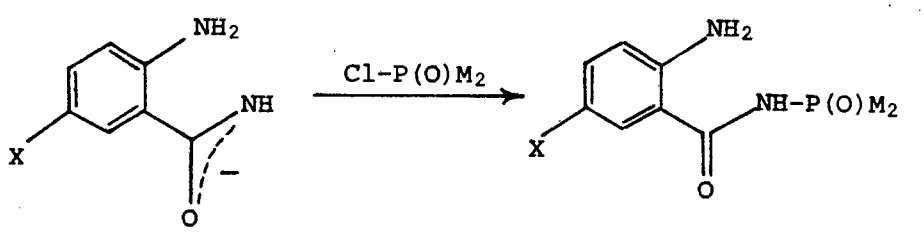
In accordance with the above observation, Ning *et al.*[47] have found that constraint of the carboxamide anion moiety in a cyclic system, leads to preferential O-phosphorylation, permitting the isolation of synthetically useful derivatives such as (2.20) (eq. 2.19):



(2.20)

[2.19]

In contrast, anions derived from acyclic amides such as the substituted anthranilamides (2.21), undergo exclusive N-phosphorylation under the identical reaction conditions (eq. 2.20):[47]

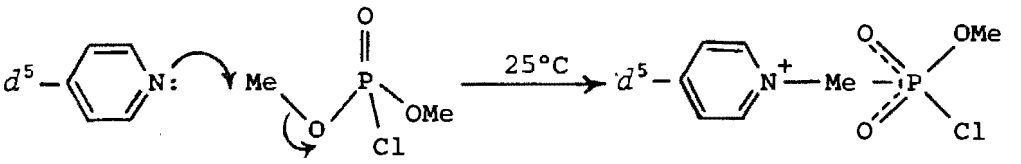


(2.21)

[2.20]

The O-phosphorylated derivative (2.20) undergoes quantitative thermal rearrangement to the N-phosphorylated isomer in mesitylene under reflux, illustrating the thermodynamic preference of the N-phosphorylation process. An investigation of the phosphorylation of a variety of urea and carbamate anions and their thio analogues has led Périé *et al.*[39] to a similar conclusion, namely initial formation of a kinetically controlled O(S)-phosphorylated product which is capable of rearranging to the thermodynamically favoured N-phosphorylated form.

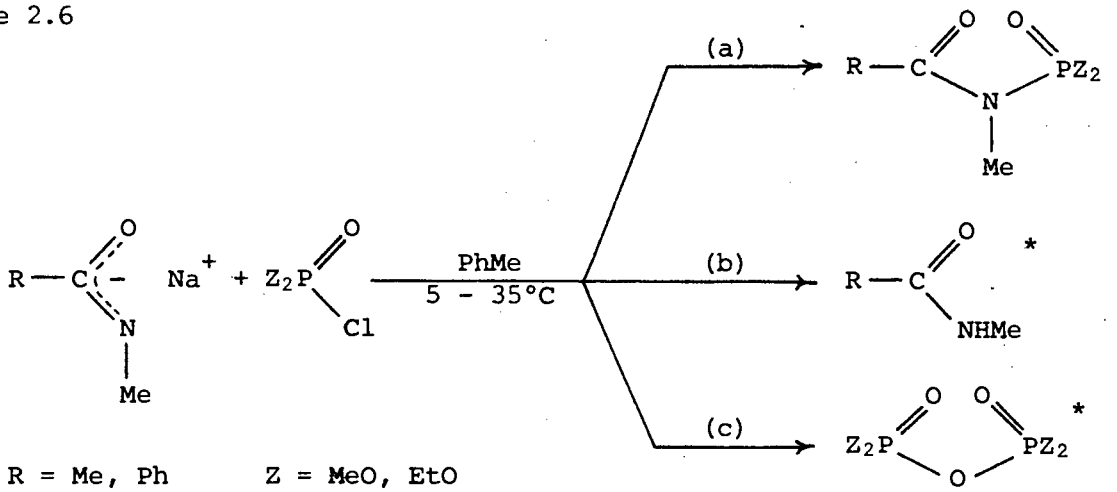
In an attempt to synthesise the mixed imide (1c), an equimolar mixture of N-methylacetamide and dimethylphosphorochloridate was heated in ether in the presence of triethylamine. Since no reaction is apparent after 40 h, the Et_3N/Et_2O was replaced by d^5-pyridine and the mixture stirred at 25°C for 24 h. The appearance of a singlet at δ 4.46 in the ^1H NMR spectrum of the product mixture, which was identified as the N-Me absorption of N-methylpyridinium ion, indicates that under these reaction conditions, pyridine acts as a stronger nucleophile than base and serves to de-methylate the phosphorylating agent (eq. 2.21):[48]



[2.21]

The phosphylation reactions were thus carried out with prior generation of the carboxamide conjugate base with metallic sodium. The sodium salts of N-methylacetamide and N-methylbenzamide were found to react smoothly with the phosphacyl halides $Z_2P(O)Cl$ at 5 - 35°C in toluene (Scheme 2.6).

Scheme 2.6



R = Me, Ph Z = MeO, EtO

Et, $\diagup CH_2O$

* Only observed for Z = MeO, EtO.

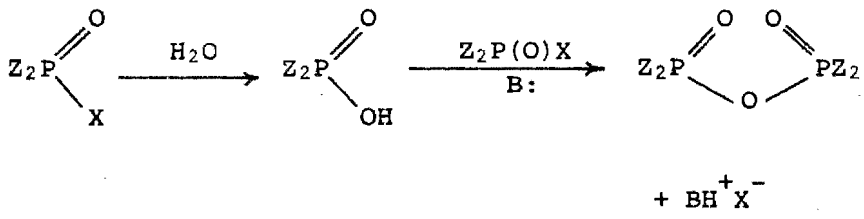
The product mixtures obtained by filtration and evaporation were analysed by TLC and ^1H NMR spectroscopy and the various mixed imides identified by their characteristic low-field N-methyl absorptions. The mixed imides were isolated from the product mixtures by column chromatography and/or fractional vacuum distillation. The structures of the products were confirmed by elemental analysis and IR and ^1H NMR spectroscopy. The percentage yields of the mixed imides obtained in this way are given in Table 2.1:

Table 2.1 Percentage yields of mixed imides $Z_2P(O)$-NMe-C(O)R.[a]

Z	R	Temp.(°C)	% Yield
MeO	Me	5 - 10	38
EtO	Me	5 - 10	34
EtO	Ph	5 - 10	30
Et	Me	5 - 10	75
$\diagup CH_2O$	Me	30 - 35	72

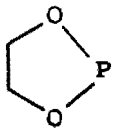
[a]Reaction conditions as described in Scheme 2.6

The yields of the three acyclic phosphoric mixed imides (1c-e) are particularly low, since their formation is accompanied by side reactions leading to large quantities of carboxylic amide and tetraalkylpyrophosphate, as illustrated in Scheme 2.6 (pathways b, c). In contrast, the analogous side reactions do not plague the syntheses of the phosphinic and cyclic phosphoric derivatives (1f, g), thus allowing mixed imide formation in much higher yield. Pyrophosphate formation has been similarly observed as a side reaction in the phosphorylation of urea and carbamate anions.[39] The authors propose that despite precautions taken to ensure anhydrous conditions, partial hydrolysis of the highly reactive phosphorylating agent $Z_2P(O)X$ is difficult to avoid and general base-catalysed pyrophosphate formation ensues (eq. 2.22):[39]



[2.22]

Assuming constant availability of atmospheric moisture throughout, the contribution of this side reaction must therefore depend upon the reactivity of $Z_2P(O)X$ with respect to hydrolysis and, in accordance with the above argument, the mixed imide syntheses (Scheme 2.6) which utilise the most reactive phosphylating agents $Z_2P(O)Cl$, should be accompanied by the formation of the largest quantities of the corresponding anhydride $(Z_2PO)_2O$. The rates of hydrolysis of the phosphylating agents decrease in the order:

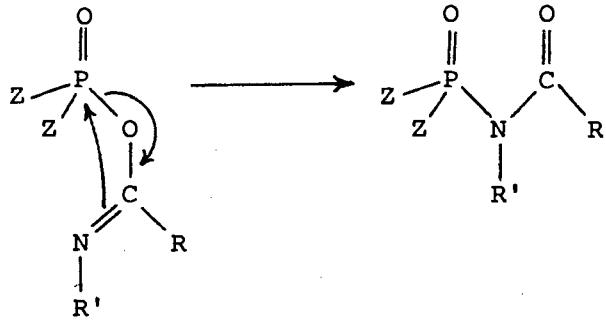


$P(O)Cl > Et_2P(O)Cl > (MeO)_2P(O)Cl > (EtO)_2P(O)Cl$.[50] The observed anhydride formation preference in the syntheses of (1c-e) which utilise the least, rather than most reactive phosphylating agents, thus contradicts the

above and argues against anhydride formation according to eq. 2.22. An alternative source of the anhydride oxygen must therefore be sought.

O-Phosphylation of a carboxamide anion $[RCONR']^-$, results in the formation of the kinetically controlled O-phosphyl imidate (2.22). Unlike their cyclic analogues, which are sufficiently stable to be isolated[46,47] (c.f. (2.20)), acyclic derivatives of this type are known to be extremely unstable and are capable of reacting in a variety of ways:

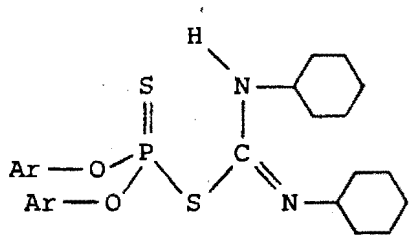
(1) O → N phosphoryl migration is believed to proceed via intramolecular nucleophilic displacement at the phosphacyl centre and results in the formation of the thermodynamically favoured N-phosphylated derivative (eq. 2.23):[51-53]



[2.23]

(2.22)

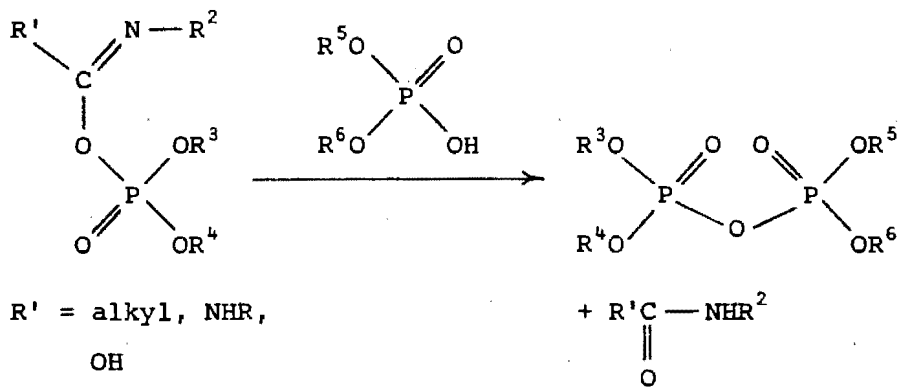
The isomerisation mechanism is analogous to that proposed for the rearrangement of O-acyl imidates to N-acyl carboxamides.[54] The observation that bulky substituents at phosphorus (Z)[53] and nitrogen (R')[51] considerably decelerate the isomerisation of (2.22), lends support to the intramolecular O → N phosphyl migration mechanism. In addition, Périé *et al.*[53] have found that the thio analogue (2.23) is protected against rearrangement by the long C — S — P distance, which results in poor overlap of the nitrogen and phosphorus orbitals. This derivative is readily isolable as its conjugate acid and has been the subject of a variety of structure[53] and reactivity[55] studies.



Ar = 2,6-diMe-C_6H_3

(2.23)

(2) O-Phosphoryl imidate formation (2.22, Z = RO) is a particularly useful means of activating phosphoric acid derivatives towards nucleophilic attack and great advantage has been taken of their powerful phosphorylating ability in the synthesis of mixed pyrophosphoric acid derivatives (eq. 2.24):[51,56]



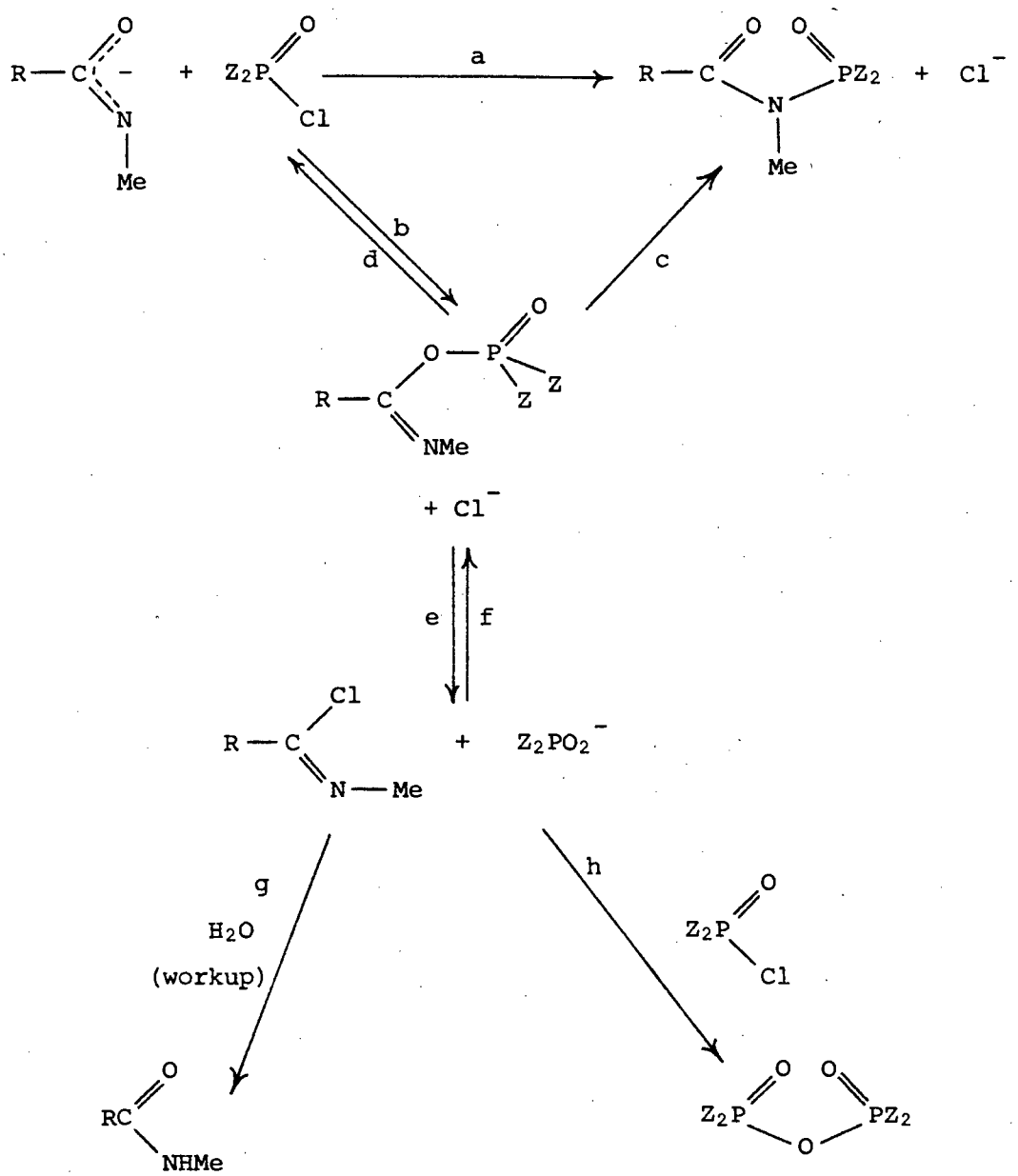
R' = alkyl, NHR, OH

+ $R'C(=O)-NHR^2$ [2.24]

(3) As indicated in equations 2.16 and 2.17 above, the imidate carbon atom of (2.22) offers an additional electrophilic centre to the molecule. Nucleophilic substitution at this site results in oxygen transfer from carbon to phosphorus and the expulsion of an azomethine-containing product. The relative contributions of nucleophilic substitution at the phosphorus and carbon centres of (2.22), obviously depend upon the relative electrophilicities of the two sites, which are in turn, dependent upon the substituents at phosphorus, carbon and nitrogen.

Scheme 2.7 summarises the situation resulting from the reaction of a carboxamide anion $[RCONMe]^-$ with a phosphylating agent $Z_2P(O)Cl$.

Scheme 2.7



Irreversible formation of the thermodynamically favoured N-phosphylated product, can arise via direct N-phosphylation of the carboxamide anion (pathway a) and via rearrangement of the O-phosphyl imidate (pathway b followed by c). However, the kinetically controlled O-phosphyl imidate is also susceptible to nucleophilic attack by Cl^- at phosphorus and carbon (pathways d and e respectively); whilst the former reaction regenerates the starting materials, the latter introduces two new species into the reaction medium.

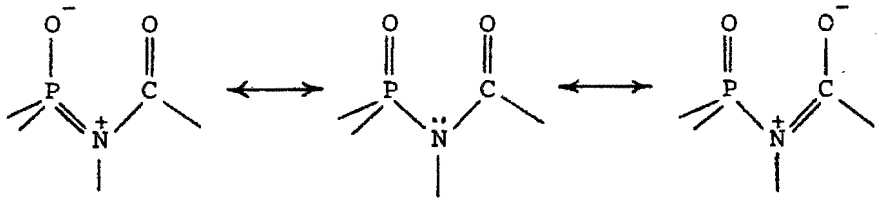
These may undergo irreversible reaction via pathways g and h, to yield carboxamide and anhydride products respectively. Scheme 2.7 thus qualitatively accounts for the formation of the three major products that are observed in this reaction (Scheme 2.6). Also apparent from Scheme 2.7, is the dependence of the product mixture composition on the reactivity of the O-phosphyl imidate towards Cl^-; predominant attack at phosphorus (pathway d) leads to mixed imide formation whereas attack at the imidate carbon (pathway e) provides a possible avenue for anhydride (and carboxamide) formation. Structural variation within the O-phosphyl imidate (R, Z) modifies the relative contributions of pathways d and e. The absence of anhydride formation in the syntheses of (1f, g) can thus be rationalised in terms of a predominance of pathway d, as a result of the facile nucleophilic substitution at the Et_2PO and centres, respectively. However, since the rate of Cl^- attack at an $(RO)_2PO$ (R = Me, Et) centre is significantly slower, a greater participation of the competitive reaction via pathway e is encouraged, thereby affording the necessary route for carboxamide and tetraalkylpyrophosphate formation. Although somewhat simplistic, Scheme 2.7 nonetheless provides an explanation of the selectivity in the side reactions observed and obviates the need to invoke partial hydrolysis of the phosphorylating agent to account for the pyrophosphate formation.

The synthesis of tertiary mixed imides from both phosphylamide and carboxamide precursors, is thus fraught with difficulties. Although the N-phosphylation of a carboxamide anion offers the most satisfactory preparative route, the possible participation of complicating side reactions, which largely arise from the ambident nucleophilicity of the carboxamide anion, leads to a lowering of yields. A careful selection of substrate structure and reaction conditions, is thus essential to ensuring efficient mixed imide formation.

CHAPTER 3

General Spectroscopic Properties

A knowledge of the electronic structure of a given system forms the foundation upon which an understanding of its chemical reactivity can be built. In Π-electron-containing systems, the extreme sensitivity of the spectroscopic properties of the molecule to changes in the Π-electronic distribution therein, is exploited for the purpose of assessing the relative contributions of the various "extreme electronic structures" or canonical forms. The Π-electron distribution within the OPNCO fragment of a mixed imide, depends upon the nature and extent of the resonance interaction of the nitrogen non-bonding electrons with the adjacent phosphyl and carbonyl centres as illustrated by the following canonical forms:



(3.1) (3.2)

The infrared (IR), ^{1}H and ^{13}C NMR spectral characteristics of the mixed imides (1) and selected related compounds, have thus been compared with the aim of establishing the relative contributions of canonical structures (3.1) and (3.2) to the overall mixed imide resonance structure.

3.1 INFRARED SPECTROSCOPY

In both phosphylamide and carboxamide systems, the IR spectral feature of greatest interest is the frequency of the X=O bond (X = P, C). This frequency is largely a function of the extent of resonance interaction within the X(O)-N moiety of the amide, with low frequencies typifying highly conjugated systems. However, in primary and secondary amides, the additional lowering influence of intermolecular hydrogen bonding on $\nu_{X=O}$, is very pronounced, and must be taken into consideration in comparative studies.

Progressive dilution of the amide in a nonpolar aprotic solvent such as carbon tetrachloride, serves to disrupt the X═O....H—N hydrogen-bonded structure and leads to a significant increase in the acyl stretching frequency.[57] This dilution principle was applied in investigating the nature of the intermolecular hydrogen bonding in the secondary mixed imide (1a). Since this compound is structurally derived from both dimethylphosphoramide and benzamide systems, the possibility of intermolecular association involving the phosphoryl and/or carbonyl groups must be taken into consideration. It was found that although the carbonyl stretching frequency is unaffected in going from the solid state (Nujol mull, 1682 cm^{-1}) to dilute solution (0.1% CCl_4 solution, 1683 cm^{-1}), the phosphoryl absorption undergoes significant changes, as illustrated in Fig. 3.1. The implication of these results is an involvement of the phosphoryl, rather than carbonyl group, in the intermolecular hydrogen bonding. Evidence in support of this conclusion is presented in Chapter 4, where the question of intermolecular hydrogen bonding has been addressed from a structural point of view.

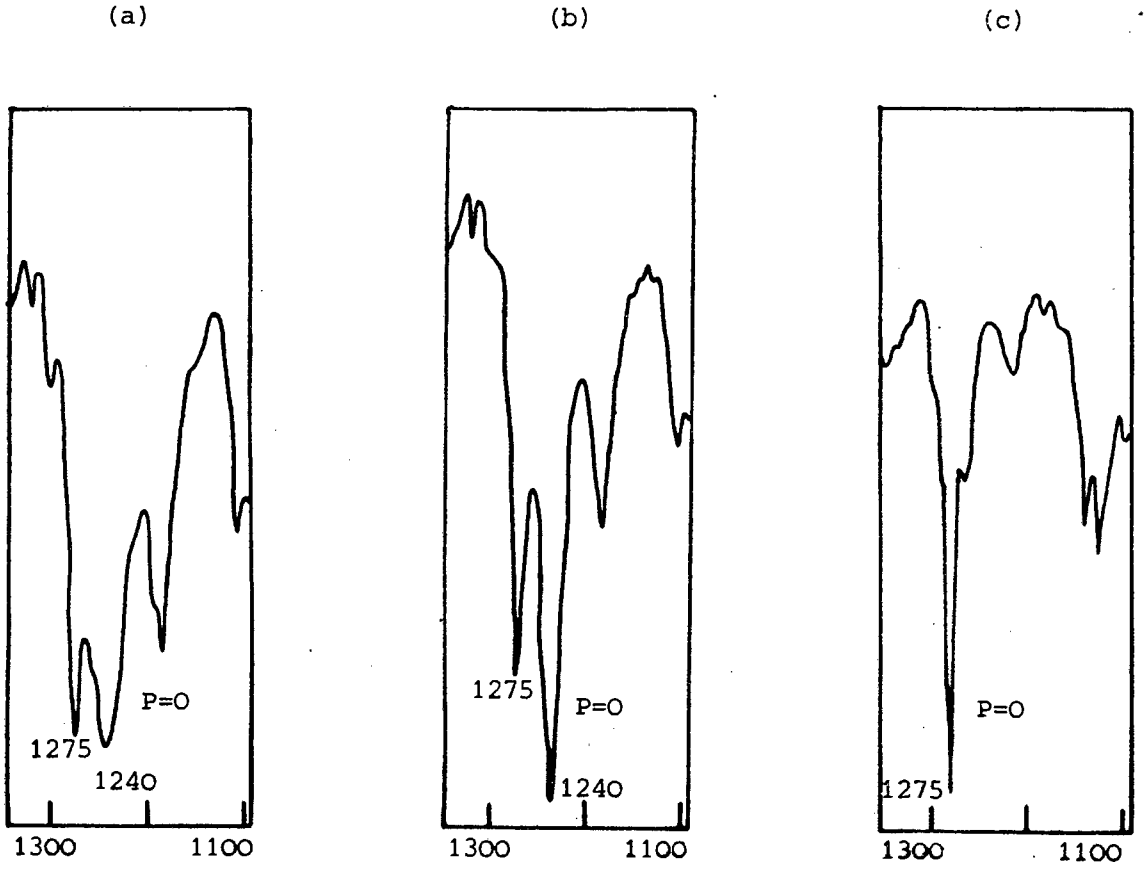
The phosphyl and carbonyl stretching frequencies of the tertiary mixed imides (1c-f) and related tertiary N-methyl carboxylic and phosphoric amides and imides are given in Tables 3.1 and 3.2, respectively. A comparison of the phosphoryl stretching frequencies of the three dimethylphosphoryl compounds given in Table 3.1, illustrates the sensitivity of $\nu_{P=O}$ to the electron-withdrawing ability of the substituent Y (Me < Ph < COMe). The phenyl and acetyl substituents can competitively resonance interact with the nitrogen non-bonding electrons, thus reducing the conjugation with the adjacent phosphoryl group. The higher $\nu_{P=O}$ value observed in the N-benzoyl mixed imide (1302 cm^{-1}) than that in its N-acetyl analogue (1295 cm^{-1}) suggests a stronger electron-withdrawing ability of a benzoyl than an acetyl substituent. The lowest $\nu_{P=O}$ value in the series given in Table 3.1 is that of the phosphinic

Figure 3.1 1300 - 1100 cm^{-1} region of the IR spectrum of N-benzoyl dimethylphosphoramidate:

(a) as a Nujol mull;

(b) as a 30% solution in CCl_4;

(c) as a 0.2% solution in CCl_4.



mixed imide (1f, 1195 cm^{-1}). This observation is consistent with the fact that the $\nu_{P=O}$ values of acyclic N-substituted dialkylphosphinamidates are at least 40 - 80 cm^{-1} lower than those of the corresponding dialkylphosphoramidates.[59] The phosphoryl stretching frequency of the cyclic mixed imide (1g, 1311 cm^{-1}) is 17 cm^{-1} higher than that of its acyclic analogue (1c, 1294 cm^{-1}). It is known that the $\nu_{P=O}$ value of a phosphate ester derivative $(RO)_2P(O)-X$ depends upon the steric bulk of the substituent R; bulky alkoxyl substituents at phosphorus cause an increase in the conical (O-P-O) angle and a subsequent decrease in the phosphoryl stretching frequency.[57] Therefore, the high stretching frequency observed for (1g) is most likely a result of a significant decrease in the conical angle upon cyclisation,[60] rather than one of abnormally extensive resonance interaction with the adjacent nitrogen atom. The conclusion that can thus be drawn from the data given in Table 3.1, is that the $\nu_{P=O}$ value is dependent upon both the nature of the substituents X at phosphorus and the conjugating ability of the substituent Y at nitrogen.

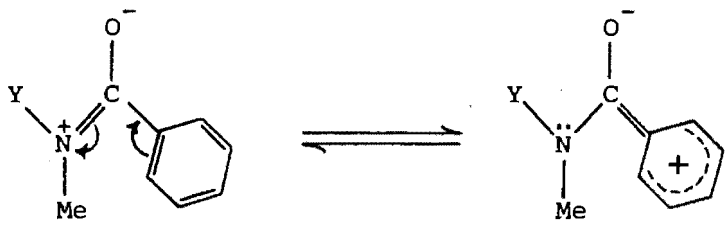
Table 3.1 Phosphyl stretching frequency ($\nu_{P=O}$) in $X_2P(O)-N(Y)Me$.[a]

Substrate	X	Y	$\nu_{P=O}$ (cm^{-1})
(1f)	Et	C(O)Me	1195
b	MeO	Me	1260
c	MeO	Ph	1275
(1c)	MeO	C(O)Me	1294
(1d)	EtO	C(O)Me	1295
(1e)	EtO	C(O)Ph	1302
(1g)	CH_2O	C(O)Me	1311

[a] Spectra recorded as 0.1 - 0.5% solutions in CCl_4;

[b] Ref. 57; [c] Ref. 58.

The effect of the nitrogen substituent Y on the carbonyl stretching frequency in the series of N-methylacetamides (X = Me) and benzamides (X = Ph) is illustrated in Table 3.2. The acetamide $\nu_{C=O}$ values are consistently lower than the benzamide values, as a result of the resonance donation of the ring, which lends additional single bond character to the carbonyl bond:



(3.3) (3.4)

A high carbonyl stretching frequency within a given series, is indicative of extensive competitive resonance interaction of the nitrogen lone pair with substituent Y. As expected, the lowest $\nu_{C=O}$ value within the series of acetamides is that of N,N-dimethylacetamide (Y = Me); replacement of the non-conjugating methyl substituent Y by competitive resonance acceptors, results in a steady increase of $\nu_{C=O}$ to a maximal value of 1707 cm^{-1} for N-methyldiacetimide (Y = COMe).

Judging by the similarity in the $\nu_{C=O}$ values of the phosphoric mixed imides (1c, d, g), it appears that the conjugating ability of a phosphoryl substituent $(RO)_2P(O)$ is only marginally dependent upon the nature of R (Me, Et, $-CH_2$). In contrast, the $\nu_{C=O}$ value of the phosphinic derivative (1f) is found to be considerably lower (1668 cm^{-1}) than the values of its phosphoric analogues (1695 - 1697 cm^{-1}), implying a significantly poorer resonance interaction between the nitrogen lone pair and an adjacent phosphinic, than phosphoric centre. This observation is consistent with the substantial difference that has been found between the σ_R° values of dialkylphosphoryl and dialkylphosphinyl substituents.[63] It is interesting to note that the resonance withdrawal of the Et_2PO substituent is even less than that

Table 3.2 Carbonyl stretching frequency ($\nu_{C=O}$) in X-C(O)-N(Y)Me[a].

Substrate	X	Y	$\nu_{C=O}$ (cm^{-1})
b	Me	Me	1660
(1f)	Me	$P(O)Et_2$	1668
c	Me	Ph	1692
(5.2b)	Me	C(O)Ph	1667/1695[d]
(1g)	Me		1695
(1c)	Me	$P(O)(OMe)_2$	1697
(1d)	Me	$P(O)(OEt)_2$	1697
(2.14a)	Me	C(O)Me	1707
(2.6)	Ph	C(NMe)Ph	1658
(2.5)	Ph	C(O)Ph	1659
(5.2b)	Ph	C(O)Me	1667/1695[d]
(1e)	Ph	$P(O)(OEt)_2$	1676

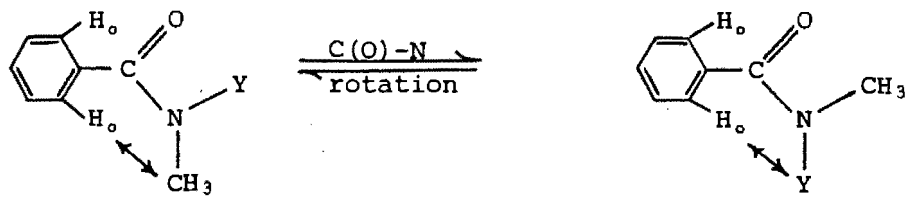
[a]Spectra recorded as 0.1 - 0.5% solutions in CCl_4;

[b]Ref. 61; [c]Ref. 62; [d]Probable assignment is 1667 cm^{-1} (ν_{COPh}), 1695 cm^{-1} (ν_{COMe}).

of a phenyl substituent at nitrogen. An N-benzoyl substituent serves to increase the acetamide carbonyl stretching frequency to a value of 1695 cm^{-1}, which is comparable with the $\nu_{C=O}$ values observed in the mixed imides (1c, d, g) (1695 - 1697 cm^{-1}), indicating a similarity in the resonance acceptance of a benzoyl and a dialkylphosphoryl substituent Y in the MeCO-N(Y)Me system. Finally, the high $\nu_{C=O}$ value observed in the symmetrical carboxylic imide (Y = COMe; 1707 cm^{-1}), suggests that an acetyl substituent is the most effective competitive resonance acceptor within the acetamide series.

An analogous comparative analysis of the carbonyl stretching frequency within the benzamide series PhCO-N(Y)Me is, however, complicated by the resonance contribution of the benzoyl ring in the form of canonical structure (3.4). Since a significant contribution of (3.4) to the overall resonance effect can only be achieved if the PhCO moiety is approximately planar, it follows that higher $\nu_{C=O}$ values can be expected to arise from sterically hindered systems, in which ring twist (about the (O)C — $C_{arom.}$ bond) is pronounced. Interatomic repulsions can, in principle, also lead to a loss of planarity of the amide moiety (rotation about the (O)C-N bond) thus resulting in a diminished contribution of canonical structure (3.3). However, since the attendant loss of resonance stabilisation (*ca.* 80 kJ mol^{-1}) in this case would certainly exceed that caused by ring twist, only very severe steric hindrance which could not be minimised by ring twist, would justify the loss of amide planarity. The mixed imide (1e) has the highest $\nu_{C=O}$ value within the benzamide series (Table 3.2). If considered in terms of resonance effects alone, the implication is that a diethylphosphoryl substituent is a better competitive resonance acceptor than an acetyl substituent, thus contradicting the results of the acetamide $\nu_{C=O}$ analysis discussed above. This apparent anomaly suggests a variation in the degree of benzoyl ring twist within the series of tertiary benzamide derivatives.

The intramolecular repulsion between the N-methyl and ortho aromatic hydrogen atoms, is common to all four benzamide derivatives assuming invariant sp^2 hybridisation of the amide nitrogen atom throughout. This results in a certain deviation of the benzoyl ring away from the plane of the amide moiety. However, rotation about the C(O)-N bond results in a *cis* orientation of the benzoyl ring and the substituent Y; the interatomic repulsions between the ortho aromatic hydrogens and the atoms of substituent Y, are dependent upon the steric bulk of the substituent and can thus vary considerably within the series:



Y-independent repulsion Y-dependent repulsion

It can be shown from molecular models that $H_o \leftrightarrow Y$ repulsions decrease in the order $(EtO)_2P(O)$ > C(NMe)Ph > C(O)Ph > C(O)Me. In accordance with the above argument, the benzoyl ring is expected to be most twisted in the mixed imide (1e), thus offering a possible explanation of its relatively high $\nu_{C=O}$ value. The question of benzoyl ring twist in the benzamide derivatives has also been analysed from a ^1H NMR spectroscopic point of view and is further discussed in the following section.

3.2 PROTON MAGNETIC RESONANCE SPECTROSCOPY

Information pertaining to molecular and electronic structure has been obtained from a comparative analysis of the ^1H NMR spectral features of the mixed imides (1) and selected related compounds. The variation in the phosphorus-hydrogen coupling constant J(PNCH) with the nature of the substituents at phosphorus (Z) and at nitrogen (Y), within a series of N-methyl phosphyl-amidates, is illustrated in Table 3.3. The observed trend indicates that the replacement of a non-conjugating nitrogen substituent (e.g. H, Me) by a competitive resonance acceptor (e.g. Ph, acyl), results in a significant lowering of the coupling constant. Analogous variations in the magnitude of the J(PNP)[67] and J(PNCH)[68] values of certain P^{III} derivatives and in the J(PNCH) values of a series of phosphoramidic chlorides[37] bearing electron-attracting substituents at nitrogen, have been previously observed. The two main factors that determine the magnitude of the J(PNCH) value in the system $Z_2P(O)N(Y)Me$ are firstly, the P-N bond order[69] and secondly, the

Table 3.3 J(PNCH) values of $Z_2P(O)-N(Y)CH_3$.

Substrate	Z	Y	J(PNCH) (Hz)
(1f)	Et	C(O)Me	6.5
a	MeO	$N=CH_2$	7.2
(1c)	MeO	C(O)Me	7.5
(1d)	EtO	C(O)Me	7.5
(1e)	EtO	C(O)Ph	8.0
b	MeO	Ph	8.0
c	Me_2N	$P(O)Cl_2$	8.2
(1g)	CH_2O	C(O)Me	9.0
d	MeO	Me	10.0
(2.1b)	MeO	H	11.0
(2.1c)	Et	H	13.0

[a]Ref. 64; [b]Ref. 65; [c]Ref. 37; [d]Ref. 66.

the hybridisation of the atoms involved.[70] A high P-N bond order is expected to enhance the J(PNCH) value as a result of the diminution of nuclear spin-spin coupling with distance.[71] In addition, increased s character of the σ bonding orbitals of the atoms involved, is expected to lead to enhanced coupling; in this respect, the hybridisation of the phosphorus atom within the series of compounds listed in Table 3.3, is assumed to be invariant and the only atom that must be considered is the nitrogen, which may be either pyramidal (sp^3, low J) or planar (sp^2, high J). The nature of the substituent Y affects both the P-N bond order and the hybridisation of the nitrogen atom. Competitive resonance-accepting substituents (e.g. Y = Ph, acyl) reduce the electron density in the P-N bond and thus decrease the J(PNCH) value. However, if the conjugation between the nitrogen atom and such a substituent Y is extensive, the nitrogen atom is forced into a planar geometry and the effect of the

increased s character of its σ bonding orbitals, is an increase in the J(PNCH) value. On the other hand, non-conjugating substituents (Y = H, Me) lead to an increase in the P-N bond order and enable the nitrogen atom to assume a more pyramidal geometry.[72] Therefore, substituent Y has two opposing effects upon the magnitude of the J(PNCH) value; the observation that electron-attracting substituents at nitrogen result in a lowering of the J(PNCH) value indicates that the P-N bond order factor is the more important in determining the coupling constant. The substituents Z at phosphorus affect the coupling by modifying the inductive and resonance electron-withdrawing ability of the Z_2PO group, which in turn influences the P-N bond order. An interesting comparison in this regard, is between the J(PNCH) values of the diethylphosphinic and dimethylphosphoric mixed imides (1f) and (1c) (6.5 and 7.5 Hz respectively). As discussed in Chapter 3.1, the IR analysis of these two compounds indicated more extensive conjugation within the NMeC(O)Me moiety of the former than the latter, owing to the difference in the resonance acceptance of the Et_2PO and $(MeO)_2PO$ substituents. The reduced availability of the nitrogen lone pair in (1f), leads to a lowering of the P-N bond order relative to that of (1c), thereby accounting for the observed difference in their corresponding J(PNCH) values.

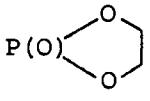
The location of a given proton resonance in the spectrum, is primarily influenced by three intramolecular factors: the inductive effect of neighbouring groups, which operates through chemical bonds, the anisotropy effects of structural units such as carbonyl and phosphacyl groups, operating through space, and the mutual deshielding influence of van der Waals repulsion. Structural variations within a given system, lead to changes in the detailed chemical environment of the proton/s in question, which in turn, affect the relative contributions of these three factors to the resonance frequency. It is therefore essential to take cognisance of such effects in comparative

chemical shift studies.

The deshielding influences of the acyl substituents X and Y (carboxyacyl, phosphacyl) on the chemical shift of the N-methyl protons (δ_{NMe}) in the system X-NMe-Y are summarised in Table 3.4. Chemical shift comparisons with the parent secondary amide systems provide a means of quantifying the deshielding effects of the various acyl substituents on the N-methyl protons. In this regard, the following decreasing trend has been observed for this system: PhCO (52 ± 8 Hz) > MeCO (38 ± 8 Hz) > $(EtO)_2PO$ (29 ± 6 Hz). The powerful deshielding influence of a benzoyl substituent, is effectively illustrated by the abnormally low δ_{NMe} value in the dibenzoyl derivative $(PhCO)_2NMe$ (δ 3.51). One of the important factors affecting δ_{NMe} in X-NMe-Y, is the inductive effect of the X(Y)N substituent, which is in turn, related to the inductive effects of the individual substituents X and Y. The overall inductive effect of X(Y)N is, however, also dependent upon the geometry of the nitrogen, which may tend towards pyramidality in the more sterically hindered systems. In addition, the N-methyl protons are in sufficiently close proximity to X and Y to be influenced by their potential anisotropic and van der Waals repulsion effects. Therefore, it is clear that in view of the diversity of factors affecting δ_{NMe}, the acyl substituent deshielding effects derived from such a comparative chemical shift analysis, are not simple reflections of their electron-withdrawing abilities.

However, an analysis of acetyl methyl chemical shift variations within the XNMe-COMe system, offers a more direct approach towards assessing the relative electron-withdrawing abilities of the various acyl substituents, since the remoteness of the variable substituent X from the site of interest, justifies ignoring variations in the anisotropic and van der Waals repulsion effects within the series (Table 3.5). The observed variation in δ_{COMe} can therefore be attributed to changes in the inductive effect brought about by

Table 3.4 N-methyl chemical shift (δ) of X-NCH$_3$-Y.

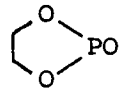
X	Y	δ (X,Y) (ppm)	Δδ (Hz)[a]
$(EtO)_2PO$	H	2.58	0
$(EtO)_2PO$	$P(O)(OEt)_2$	2.97	39
MeCO	H	2.78	0
MeCO	COMe	3.22	44
MeCO	COPh	3.18	40[b] 24[c]
MeCO	$P(O)(OMe)_2$	3.05	27
MeCO	$P(O)(OEt)_2$	3.04	26[b] 46[c]
MeCO		3.23	45
MeCO	$P(O)Et_2$	3.15	37
PhCO	H	2.94	0
PhCO	COPh	3.51	57
PhCO	$P(O)(OEt)_2$	3.18	24[b] 60[c]

[a] Downfield shift relative to parent secondary amide;

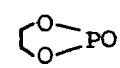
[b] $\Delta\delta = \delta(X,Y) - \delta(X,H)$;

[c] $\Delta\delta = \delta(X,Y) - \delta(H,Y)$.

Table 3.5 Acetyl methyl chemical shift (δ) of XNMe-$COCH_3$.

X	δ (ppm)	Δδ (Hz)[a]
H	2.01	0
Et_2PO	2.25	24
	2.29	28
PhCO	2.32	31
$(MeO)_2PO$	2.39	38
$(EtO)_2PO$	2.39	38
MeCO	2.42	41

[a]Downfield shift relative to MeCONHMe

substituent X. As discussed in Chapter 3.1, the resonance-accepting ability of X in the system XNMe-COMe determines the availability of the nitrogen non-bonding electrons for resonance interaction with the adjacent acetyl group, thereby influencing the electron density at the carbonyl carbon atom. Strongly conjugating substituents X, increase the electrophilicity of this atom and thus enhance the inductive withdrawal of the XN(Me)CO substituent, resulting in a deshielding of the methyl protons. According to this argument, the conjugating abilities of the various substituents X given in Table 3.5, increase in the order: Et_2PO <  < PhCO < $(MeO)_2PO \cong (EtO)_2PO$ < MeCO. This order is in excellent agreement with that independently obtained from the acetamide carbonyl stretching frequency analysis discussed above (Table 3.2).

The chemical shifts of the aromatic protons of a series of secondary and tertiary N-substituted benzamides are given in Table 3.6. The feature common to all the secondary derivatives, is the difference of 50 - 80 Hz in

the chemical shift between the ortho protons, which resonate as a doublet of doublets (J_{ortho} 8 Hz, J_{meta} 2 Hz) and the remaining meta and para protons, which resonate as an overlapping multiplet. However, as indicated in Table 3.6, replacement of a hydrogen substituent at nitrogen by a methyl, dramatically reduces, and in some cases, completely eliminates this chemical shift difference by shielding the ortho protons to such an extent, that their signal overlaps with those of the meta and para protons. The absorption pattern exhibited by the aromatic protons of the secondary benzamides, is typical of carbonyl-substituted aromatic compounds and can be attributed to the deshielding of the ortho protons caused by the anisotropy of the carbonyl group, as illustrated in Fig. 3.2. The angle between the planes of the aromatic ring and the carbonyl group is largely determined by the steric interaction between the ortho aromatic protons H_o and substituent X. Since the secondary benzamides (X = NHR) are relatively unhindered, coplanarity is preferred, enabling the ortho protons to lie within the deshielding cone extending from the carbonyl oxygen. The shielding of the ortho protons that is observed in going to the tertiary series (X = N(Me)R),

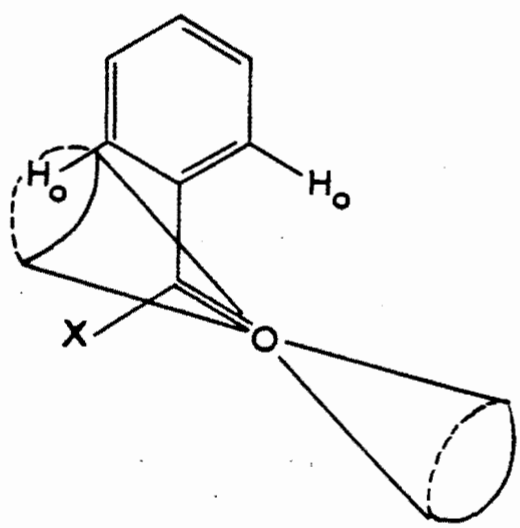


Figure 3.2 **The anisotropy of the carbonyl group.**

thus implies a movement of H_o out of the deshielding cone upon replacement of an N-H by an N-Me substituent. As discussed above (Chapter 3.1), co-planarity is disfavoured in the tertiary derivatives, owing to the more severe $H_o \leftrightarrow X$ repulsion and results in a staggering of the ring and carbonyl planes by rotation about the $C_{arom.}$—C(O) bond. This in turn, leads to a removal of H_o from within the deshielding cone and a subsequent merging of the ortho, meta and para ring proton chemical shifts.

Table 3.6 Aromatic proton chemical shifts of Ph-CO-X.

X	δ_{ortho} (ppm)	$\delta_{meta,para}$ (ppm)
NHMe	7.82	7.2 - 7.5
NHCOPh	7.85	7.3 - 7.6
$NHPO(OMe)_2$	8.12	7.3 - 7.6
$NHPO(OEt)_2$	8.16	7.3 - 7.6
$NP(OMe)_2(OEt)$	8.18	7.2 - 7.5
NMeCOPh	7.50	7.1 - 7.3
NMeCOMe	7.4 - 7.7	
$NMePO(OEt)_2$	7.3 - 7.6	
NMeC(NMe)Ph	7.2 - 7.8	

3.3 CARBON-13 MAGNETIC RESONANCE SPECTROSCOPY

The ^{13}C NMR chemical shifts of selected benzamide and acetamide derivatives are given in Table 3.7. The relative electrophilicities of the carbonyl carbon atoms in the system XCO-NR-Y, are reflected in their ^{13}C NMR chemical shifts. In accordance with expectation, acyl substituents Y deshield the carbonyl carbon by competitive resonance interaction with the nitrogen non-bonding electrons. A comparison of the $\delta^{13}\underline{C}O$ values of the MeCO-NMe-Y derivatives (Y = COPh, COMe; 172.70, 172.96 ppm respectively) indicates a

greater acetyl carbon electrophilicity in the symmetrical imide $(MeCO)_2NMe$, implying stronger resonance interaction between nitrogen and an adjacent acetyl than benzoyl group. This supports the independently reached conclusions based on comparative stretching frequency and acetyl methyl chemical shift (^1H) analyses (Tables 3.2, 3.5). However, analogous information cannot be obtained from the $\delta^{13}\underline{C}O$ values of the PhCO-NMe-Y derivatives (Y = COPh, COMe, $PO(OEt)_2$; 173.61, 173.61, 172.76 ppm respectively), owing to the complicating influence of variable conjugation between the ring and the carbonyl group, on $\delta^{13}\underline{C}O$. Of particular interest, is the dramatic deshielding of the tertiary mixed imide (1e) carbonyl carbon (172.76 ppm) relative to that of the secondary derivative (1a) (168.36 ppm; $\Delta\delta^{13}\underline{C}O$ = 4.40 ppm). The introduction of a methyl group at nitrogen may influence $\delta^{13}\underline{C}O$ by firstly, altering the hybridisation of the nitrogen atom and secondly, inducing benzamide ring twist in order to minimise steric repulsions. Information pertaining to the latter effect is contained in the ring carbon chemical shifts; it has been found that in substituted aromatic systems Ph-Z, the meta and para carbon atoms are essentially free of magnetic anisotropy effects of substituent Z,[74] and can thus be used as a sensitive tool for investigating the polar effects of Z.[63] The meta and para carbons of the secondary mixed imide (1a), are found to be 1.04 and 2.14 ppm downfield respectively, from the corresponding ring carbons of the tertiary analogue (1e), suggesting more extensive electron donation from the ring to the carbonyl group in the former, than in the latter. Significant conjugation between the ring and the carbonyl group in the Ph-CON(R)Y system (requiring PhCO planarity) serves to deshield the para, and to a lesser extent, the meta ring carbons (relative to benzene) and shields the carbonyl carbon. The high-field meta and para carbon, and corresponding low-field carbonyl carbon chemical shifts of the tertiary mixed imide (1e), are therefore consistent with a poorly conjugated PhCO moiety, i.e. significant ring twist. Inspection

of their ring and carbonyl carbon chemical shifts, reveals that the tertiary benzamide derivatives Ph-CON(Me)Y (Y = PhCO, MeCO) exhibit a similar, albeit less pronounced, tendency towards poor conjugation within the PhCO moiety. Carbon-13 NMR spectroscopy therefore affords evidence supporting the proposal of benzamide ring twist in sterically hindered derivatives Ph-CON(Me)Y, to account for the merging of the ortho, meta and para ring proton chemical shifts (Table 3.6).

N-Acylation leads to a significant downfield shift of the N-methyl carbon ($\delta^{13}\underline{C}H_3N$); the observed trend qualitatively resembles that obtained by comparing the N-methyl proton shifts (Table 3.4). The similarity in the $\delta^{13}\underline{C}H_3N$ values of the tertiary derivatives given in Table 3.7 (R = Me; 31.33 - 33.46 ppm), is indicative of invariant nitrogen atom hybridisation within the series. CNDO/2 calculations, microwave spectroscopic and X-ray crystallographic studies, have revealed a preference for planarity of the CONCO moiety in carboxylic imides, as a result of the resonance stabilisation which may be thereby gained.[75] Owing to the considerable similarity in the spectroscopic properties of the mixed imides and their symmetrical carboxylic analogues, it seems likely that both the secondary and tertiary mixed imides (1a-g), preferentially adopt a planar PONCO moiety.

In an attempt to estimate the rotational energy barriers about the P(O)-N and N-C(O) bonds of the mixed imides (1a-g), their ^{1}H NMR spectra were recorded in d^6-acetone between -10 and -90°C, with the hope of observing spectral changes. However, none of the proton absorptions of (1a-g) showed signs of broadening within this temperature range, indicating that their barriers to stereomutation are low. Low rotational energy barriers about the P(O)-N bonds of the mixed imides and indeed, of phosphylamides in general, are consistent with the extremely low torsional barriers of monophosphazenes $Z_3P{=\!=}NR$ (Z = alkyl, O-,N-alkyl; R = alkyl; $\Delta G^{\ddagger}_{P=N} < 30$ kJ mol^{-1}).[76] Dynamic ^{1}H NMR spectroscopy has, however, been employed to

Table 3.7 ^{13}C Chemical shifts (ppm) of *ca.* 0.5 M XCO-NR-Y in d^6-DMSO.[a]

X	Y	R	C_{ipso}	C_{ortho}[d]	C_{meta}[d]	C_{para}	C=O	NCH_3	$COCH_3$
Ph	Me	H	134.77	128.10	127.00	130.82	166.81	26.09	-
Ph	P(O)(OMe)$_2$	H	133.15	128.36		132.57	168.36	-	-
Ph	P(O)(OEt)$_2$	Me	136.52	127.71	127.32	130.43	172.76	33.46	-
Ph	C(O)Me	Me	135.67	128.49	128.10	131.79	173.61[b] 172.70[c]	33.53	25.24
Ph	C(O)Ph	Me	135.67	128.42	128.30	131.66	173.61	33.92	-
Me	C(O)Me	Me	-	-	-	-	172.96	31.33	25.89

[a]Under these conditions, $\delta^{13}C$(benzene) = 128.23 ppm; spectra recorded at 40°C;

[b]Benzoyl; [c]Acetyl; [d]The C_{ortho} and C_{meta} resonances were not distinguished from one another.

investigate the stereomutation of carboxylic imides, yielding $\Delta G^{\ddagger}_{N\text{-}C(O)}$ values (determined from the topomerisation rate at the coalescence temperature, T_c) ranging from 30 - 55 kJ mol^{-1}.[75] N-Acylation of a carboxamide therefore reduces the N-C(O) torsional barrier by approximately one half, as a result of competitive resonance interaction with the nitrogen non-bonding electrons. The absence of signal broadening of the mixed imides at -90°C is therefore indicative of an analogous lowering of the N-C(O) torsional barrier upon N-phosphylation of the carboxamide. A lower freezing solvent than d^6-acetone is obviously required, in order to apply dynamic NMR spectroscopy to investigate this problem more precisely.[77]

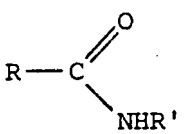
The various forms of spectroscopy are unanimous in their indication of unsymmetrical Π-electron distribution within the OPNCO mixed imide skeleton, with preferential delocalisation of the nitrogen non-bonding electrons into the N-C(O), rather than P(O)-N bond; resonance structure (3.2) therefore predominates over (3.3). However, the electron-withdrawing ability of an N-phosphyl substituent is nonetheless considerable, and leads to a significant weakening of the N-C(O) bond strength and subsequent enhancement of the electrophilicity of the carbonyl centre. The spectroscopic properties of the mixed imide system, therefore suggest the likelihood of a modification of its chemical reactivity with respect to that of its parent phosphylamide and carboxamide systems.

CHAPTER 4

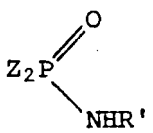
The Molecular and Crystal Structure of N-Benzoyl Dimethylphosphoramidate

4.1 INTRODUCTION

X-Ray diffraction analysis essentially involves the determination of bond lengths and angles, the evaluation of conformational preferences in the solid state and the elucidation of crystal packing modes. The technique has been extensively applied to molecular and crystal structure studies of carboxylic amides (4.1);[78] the dependence of the various structural parameters on the nature of the substituents R and R' can be evaluated by making the relevant comparisons. In contrast, structural studies on phosphylamides (4.2) are much more scarce and the recent investigation conducted by du Plessis *et al.*[79] constitutes the only systematic study of structural variation within this class of compounds.



(4.1)

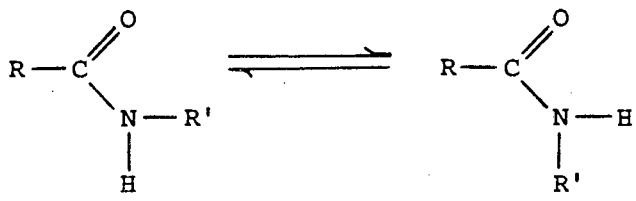


(4.2)

Spectroscopic analysis (UV, IR, NMR, microwave) of an amide establishes the the electronic structure of the system, inherent in which is the nature and extent of resonance interaction between the non-bonding electron pair on nitrogen and the adjacent acyl centre. Extensive p-orbital overlap of the nitrogen and carbonyl carbon atoms in (4.1) results in a strengthening of the amide bond, as exhibited by nitrogen-acyl bond rotational energy barriers of the order of 80 kJ mol^{-1}.[3] The structural corollaries of the Π-electron delocalisation are planarity of the NCO fragment and a shortening of the N-C bond, with concomitant lengthening of the carbonyl bond. The nature of the interaction in the phosphylamide system is necessarily different, by virtue of the non-degeneracy of the orbitals involved (2p and 3d) and the observation that the corresponding rotational energy barriers in phosphylamides

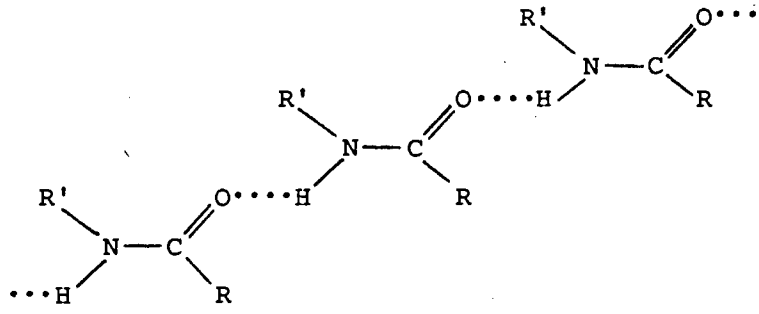
weaker.[50] However, the P-N bond length variations observed by du Plessis *et al.*[79] within a series of N-aryl phosphoramidates, indicate that albeit weak, the interaction is nonetheless sufficient to effect structural changes.

X-Ray diffraction analysis has revealed that secondary carboxylic amides (4.1; R' = alkyl, aryl) preferentially adopt the *trans* conformation (4.1a) which, on steric grounds, is thermodynamically favoured over the corresponding *cis* conformation (4.1b), by a few kJ mol^{-1}.[81]



(4.1a) (4.1b)

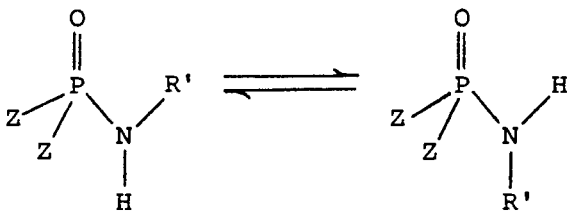
The conformational preference determines the mode of intermolecular association via C=O ... H—N hydrogen bonding and hence the crystal structure of the amide. Molecules of (4.1a) associate into polymeric aggregates, a common form of which is illustrated by (4.3), whereas (4.1b) is capable of forming hydrogen-bonded dimers.



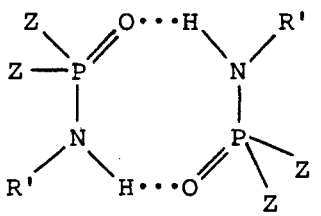
(4.3)

The tetrahedral geometry of the phosphorus atom in phosphacyl systems, allows secondary phosphylamides (4.2) to adopt the *cis* conformation (4.2b) without suffering the steric hindrance inherent in the analogous carboxylic conformation (4.1b). The energetic similarity between the conformations

(4.2a) and (4.2b) thus enables phosphylamides to show a greater tendency towards dimeric association (4.4) than their carboxamide analogues.



(4.2a) (4.2b)

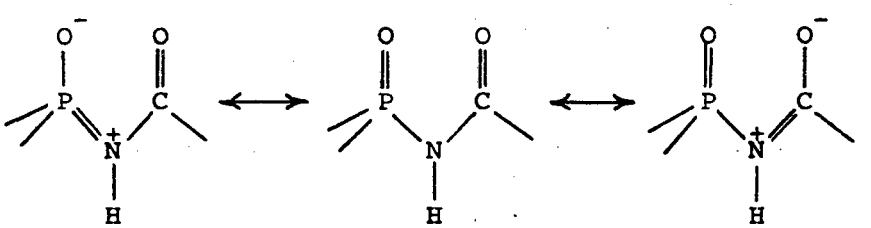


(4.4)

Previous investigation has illustrated a prevalence of the dimeric hydrogen-bonded structure (4.4) in the solid state[79] and its persistence even in dilute solution.[58,82]

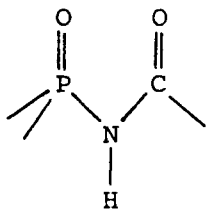
The molecular and crystal structure determination of N-benzoyl dimethylphosphoramidate,[83] which belongs to both amide systems (4.1) and (4.2) was undertaken with the following objectives in mind:

1. To determine the geometry of the phosphoric-carboxylic imide moiety and, by means of a comparative bond length analysis, investigate the nature and extent of the resonance interaction within the OPNCO fragment. In conjunction with the spectroscopic results discussed in Chapter 3, the relative contributions of resonance structures (4.5) and (4.6) can thus be evaluated.



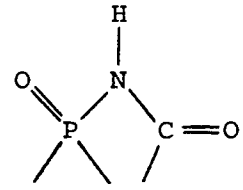
(4.5) (4.6)

2. To determine the orientation of both the phosphoryl and carbonyl dipoles with respect to the N-H bond and thus determine the conformational preference of the mixed imide:



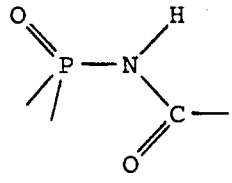
'trans-trans'

(Z,Z)



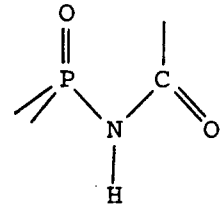
'cis-cis'

(E,E)



'cis-trans'

(E,Z)



'trans-cis'

(Z,E)

3. To establish the hydrogen bonding pattern of a system in which both phosphoryl and carbonyl oxygen atoms can compete for proximity to the amine hydrogen of a neighbouring molecule.

4.2 SOLUTION AND REFINEMENT OF THE STRUCTURE

The compound was prepared according to the literature procedure[15] (see Chapter 9). Colourless needle-like crystals were obtained by recrystallisation from petroleum ether-acetone (4:1, v/v). Preliminary oscillation, Weissenberg and precession photographs gave the space group $P2_1/n$. Data were collected by the ω-2θ scan technique on a Philips PW1100 four-circle diffractometer with graphite-monochromated MoK_α radiation (λ = 0.7107 Å). During the data collection, three reference reflections were periodically monitored to check crystal stability. Lorentz-polarisation corrections were

applied, but absorption corrections ignored.

The structure was solved by the automatic centrosymmetric routine of the SHELX[84] program system. An E-map yielded the positions of 13 of the 15 non-hydrogen atoms. A subsequent difference electron density map based on the coordinates of these atoms, revealed the positions of the remaining two carbon atoms. This was followed by a difference electron density map in which all the non-hydrogen atoms were treated anisotropically, with the methyl hydrogens refined as a rigid group and the aromatic hydrogens constrained at 1.08 Å from their respective carbon atoms, their positions being dictated by the geometry of the molecule. This yielded the position of the amine hydrogen, which was constrained at 1.00 ± 0.01 Å from the nitrogen atom and the refinement procedure carried out as above, giving a final R-index of 0.058. The crystal data and refinement parameters for the structure determination are given in Table 4.1. The final fractional atomic coordinates and anisotropic temperature factors* are given in Tables 4.2 - 4.4. The program XANADU[85] was used to calculate geometrical parameters and molecular illustrations and projections were produced by the program PLUTO.[86]

*Anisotropic temperature factors are of the form:

$$T = \exp\left[-2\Pi^2(U11h^2a^{*2} + U22k^2b^{*2} + U33l^2c^{*2} + 2U23klb^*c^* + 2U13hla^*c^* + 2U12hka^*b^*)\right]$$

Table 4.1 Crystal data and experimental and refinement parameters for structure determination.

Crystal Data	
Molecular formula	$C_9H_{12}NO_4P$
M_r	229.17
Space group	$P2_1/n$
a	8.080(4) Å
b	22.16(1) Å
c	6.347(3) Å
β	90.78(2)°
V	1136.1(9) $Å^3$
D_c	1.34 Mgm^{-3} for Z=4
$\mu(MoK_\alpha)$	0.190 mm^{-1}
F(000)	480
Data collection	
Crystal dimensions	0.9 x 0.6 x 0.9 mm
Scan mode	ω-2θ
Scan width	1.2°θ
Scan speed	0.04°θ s^{-1}
Range scanned (2θ)	6 - 46°
Stability of standard reflections	<1.0%
Number of reflections collected	1627
Number of 'observed' reflections	1410 with I(rel) > 2σI(rel)
Final refinement	
Number of variables	148
$R = \Sigma\|\|F_o\|-\|F_c\|\|/\Sigma\|F_o\|$	0.058
$R_w = \Sigma w^{\frac{1}{2}}\|\|F_o\|-\|F_c\|\|/\Sigma w^{\frac{1}{2}}\|F_o\|$	0.059
Weighting scheme, w	$(\sigma^2F)^{-1}$
U (aromatic H)	0.103 $Å^2$
U (methyl H)	0.216 $Å^2$
U (amine H)	0.098 $Å^2$

Table 4.2 Fractional atomic coordinates ($x10^4$) of the heavy atoms with e.s.d.'s.

	x	y	z
P(1)	7505(2)	390(1)	-880(2)
O(1)	6956(5)	-95(2)	503(7)
O(2)	8468(5)	192(2)	-2871(7)
O(3)	8785(5)	833(2)	60(7)
O(11)	7166(5)	1479(2)	-3580(7)
N(1)	5832(6)	777(2)	-1645(8)
C(1)	5854(7)	1286(3)	-2933(9)
C(11)	4246(7)	1563(2)	-3471(9)
C(12)	2784(8)	1461(3)	-2404(10)
C(13)	1321(9)	1736(3)	-3030(12)
C(14)	1314(9)	2128(3)	-4740(12)
C(15)	2755(10)	2238(4)	-5825(13)
C(16)	4207(9)	1960(3)	-5186(11)
C(7)	7795(12)	-304(4)	-4155(13)
C(8)	8396(13)	1161(4)	1987(13)

Table 4.3 Fractional atomic coordinates ($x10^3$) of the hydrogen atoms.

	x	y	z
H(1)	489	52	883
H(12)	279	116	894
H(13)	20	165	782
H(14)	17	234	476
H(15)	275	255	286
H(16)	533	205	396
H(71)	864	-46	465
H(72)	655	-31	521
H(73)	787	-60	719
H(81)	970	125	-225
H(82)	787	98	-341
H(83)	778	158	-157

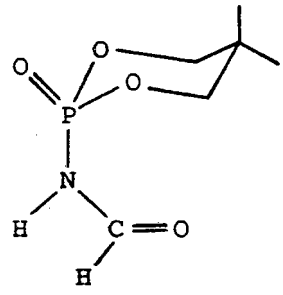
Table 4.4 Anisotropic temperature factors ($Å^2$ x 10^3) of the heavy atoms with e.s.d.'s.

	U11	U22	U33	U23	U13	U12
P(1)	38(1)	41(1)	42(1)	6(1)	2(1)	-5(1)
O(1)	45(3)	54(3)	65(3)	29(2)	1(2)	-2(2)
O(2)	55(3)	52(3)	54(3)	-8(2)	14(2)	0(2)
O(3)	47(3)	64(3)	52(3)	0(2)	5(2)	-13(2)
O(11)	46(3)	47(3)	61(3)	15(2)	8(2)	-10(2)
N(1)	40(3)	40(3)	46(3)	9(2)	2(2)	-5(2)
C(1)	47(4)	32(3)	39(3)	1(3)	2(3)	-7(3)
C(11)	45(4)	28(3)	44(3)	3(3)	3(3)	-4(3)
C(12)	51(4)	40(4)	61(4)	11(3)	9(3)	3(3)
C(13)	51(4)	48(4)	84(5)	10(4)	10(4)	7(3)
C(14)	58(5)	49(4)	85(6)	5(4)	-7(4)	7(4)
C(15)	76(6)	68(5)	82(6)	31(4)	3(5)	15(4)
C(16)	57(5)	61(5)	69(5)	22(4)	11(4)	6(4)
C(7)	112(7)	84(6)	68(6)	-27(5)	3(5)	-3(5)
C(8)	122(8)	97(7)	62(5)	-32(5)	-9(5)	-13(6)

4.3 RESULTS AND DISCUSSION

A perspective view of the compound is given in Fig. 4.1, indicating the atomic nomenclature. The bond lengths and principal bond angles are given in Tables 4.5 and 4.6 respectively.

The P-N bond distances of phosphylamides $Z_2P(O)$-NHR', have been found to be significantly shorter than the "pure single" P-N bond distance of 1.77 - 1.79 Å observed in the zwitterionic form of phosphoramidic acid $\bar{O}_3P$-NH_3^+,[87] but longer than the lower limit of 1.60 Å found in cyclotriphosphazenes,[88] in which extensive p_π-d_π interaction is evident. When compared with a series of N-aryldimethylphosphoramidates,[79] the P-N bond distance of the mixed imide (1.67 Å) is found to be relatively long, as indicated in Table 4.7. This observation is consistent with the fact that an N-benzoyl substituent is a better competitive electron sink for the nitrogen non-bonding electrons than an N-aryl substituent. In their determination of the molecular and crystal structure of the related "mixed imide", 2-formylamino-2-oxo-5,5-dimethyl-1,3,2-dioxaphosphorinane (4.7), Cameron and Karolak-Wojciechowska[89] found an unusually long P-N distance of 1.70 Å and have offered an analogous explanation in terms of the powerful electron-withdrawing ability of the formyl substituent at nitrogen.



(4.7)

The trend and wide range (0.6 Å) of P-N bond distances shown in Table 4.7 illustrate the sensitivity of this particular structural parameter to the electronic distribution within the phosphoric amide system. An analogous

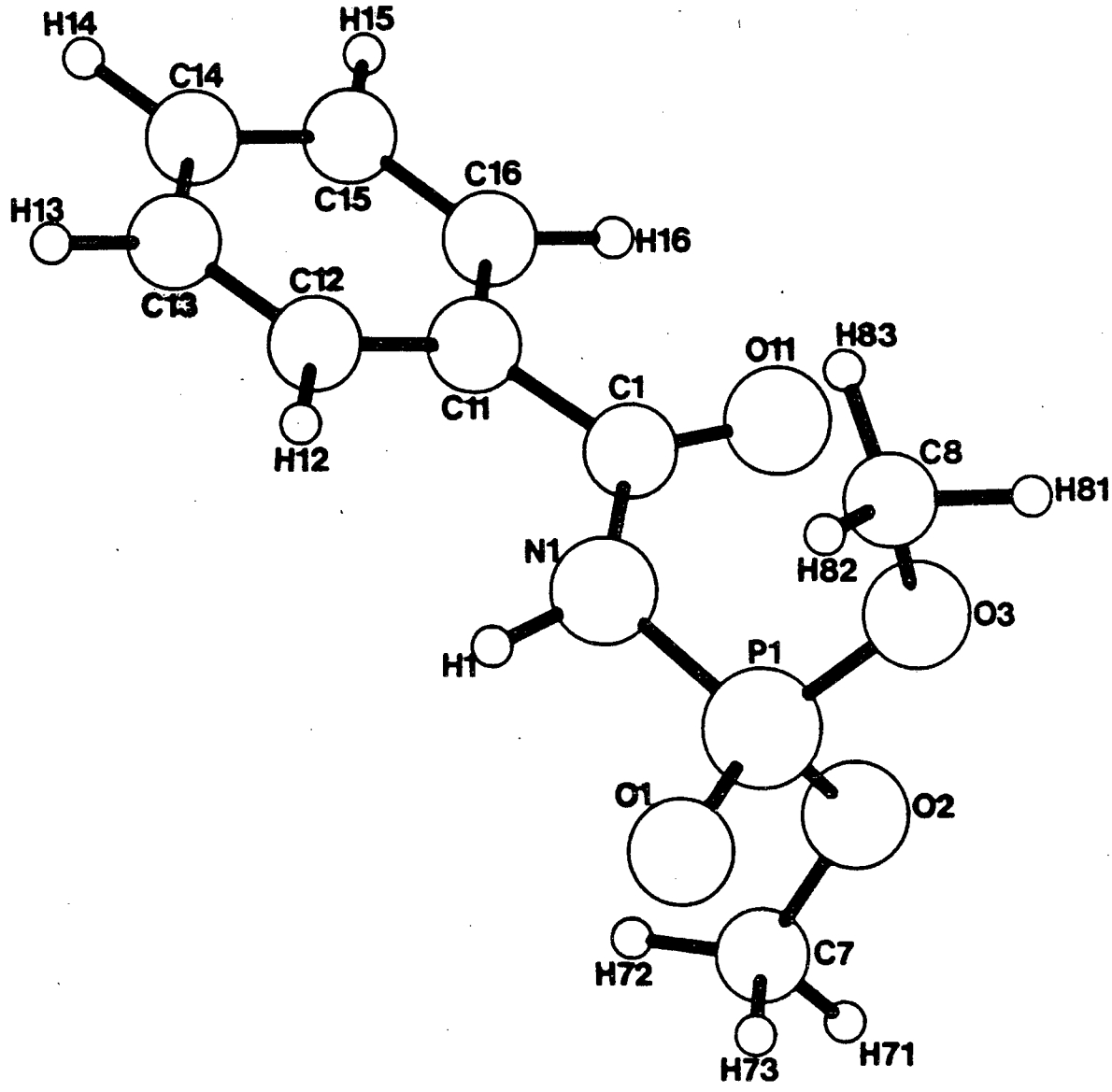


Figure 4.1 A perspective view of N-benzoyl dimethylphosphoramidate.

Table 4.5 Bond lengths (Å) with e.s.d.'s.

P(1) - O(1)	1.461(4)
P(1) - O(2)	1.557(4)
P(1) - O(3)	1.540(4)
P(1) - N(1)	1.667(5)
C(1) - N(1)	1.393(7)
C(1) - O(11)	1.219(6)
C(1) - C(11)	1.473(8)
C(11) - C(12)	1.388(8)
C(12) - C(13)	1.383(9)
C(13) - C(14)	1.391(9)
C(14) - C(15)	1.382(10)
C(15) - C(16)	1.381(9)
C(11) - C(16)	1.400(8)
O(2) - C(7)	1.468(8)
O(3) - C(8)	1.461(9)

Table 4.6 Principal bond angles (°) with e.s.d.'s.

O(1) - P(1) - O(2)	116.1(3)
O(1) - P(1) - O(3)	116.3(3)
O(2) - P(1) - O(3)	98.8(2)
N(1) - P(1) - O(1)	107.5(2)
N(1) - P(1) - O(2)	108.7(3)
N(1) - P(1) - O(3)	108.9(2)
P(1) - N(1) - C(1)	124.7(4)
N(1) - C(1) - O(11)	120.0(5)
C(11) - C(1) - O(11)	122.9(5)
C(11) - C(1) - N(1)	117.1(5)
C(12) - C(11) - C(1)	124.9(5)
C(16) - C(11) - C(1)	117.0(5)
C(16) - C(11) - C(12)	118.1(6)
C(11) - C(12) - C(13)	121.2(6)
C(12) - C(13) - C(14)	119.6(4)
C(13) - C(14) - C(15)	120.2(7)
C(14) - C(15) - C(16)	119.6(7)
C(15) - C(16) - C(11)	121.3(5)
P(1) - O(2) - C(7)	118.4(5)
P(1) - O(3) - C(8)	119.4(5)

Table 4.7 Selected crystallographic parameters of the system $(MeO)_2P(O)-NH-Y$.[a]

Y

Parameter	Ph	2-Et-C_6H_4	4-MeO-C_6H_4	2,6-diMe-C_6H_4	4-NO_2-C_6H_4	COPh
P=O (Å)	1.46	1.46	1.46	1.45	1.46	1.46
P-N (Å)	1.61	1.63	1.63	1.62	1.64	1.67
O-P-N (°)	111.0	110.5	111.1	113.2	109.4	107.5

[a]Data taken from Refs. 79 and 83.

Table 4.8 Selected crystallographic parameters of the system $PhC(O)-NH-X$.[b]

X

Parameter	H	Me	4-MeO-C_6H_4	4-NO_2-C_6H_4	P(O)$(OMe)_2$
C=O (Å)	1.24	1.24	1.22	1.23	1.22
C-N (Å)	1.31	1.33	1.36	1.38	1.39
O-C-N (°)	122	123	124	122	120

[b]Data taken from Refs. 79 and 83.

comparison of N-C bond distances of the mixed imide and a series of N-substituted benzamides, is shown in Table 4.8. The relatively long N-C bond distance of the mixed imide (1.39 Å) is comparable to that of N-p-nitrophenylbenzamide (1.38 Å), implying a similarity in the electron-withdrawing abilities of the dimethylphosphoryl and p-nitrophenyl substituents. As above, the diversity of N-C bond lengths within the series of compounds given in Table 4.8 (0.8 Å), illustrates the significant response of this structural parameter to the substituent electronic effects. The conclusion that can be drawn from these comparative bond length analyses, is predominant resonance interaction of the nitrogen non-bonding electrons with the benzoyl group, in spite of the strong inductive electron-withdrawing effect of the dimethylphosphoryl substituent, i.e. a predominance of resonance structure (4.6). This conclusion is in agreement with those independently reached by the IR spectroscopic analysis of the mixed imides (Chapter 3) and the ^{13}C NMR spectroscopic investigation of N-acylated and N-phosphorylated aniline derivatives.[11]

A consequence of classical resonance interaction within the OXN (X = C,P) fragment of an amide system, is a reciprocal relationship between the X=O and X-N bond lengths.[79] The apparent insensitivity of both carbonyl and phosphoryl bond lengths within the series of compounds given in Tables 4.7 and 4.8 respectively, to the nature of the substituent at nitrogen, is therefore difficult to rationalise in terms of Π-electron resonance effects alone. However, the influence of such factors as intermolecular hydrogen bonding, other secondary interactions and planarity distortions on solid state structural parameters such as bond lengths, can be considerable, and must be taken into account when making comparisons of this type. In addition, the contribution of a hexavalent phosphoric amide resonance structure $Z_2\bar{P}(O)=\overset{+}{N}HR'$, in which the negative charge localisation is at

phosphorus rather than oxygen, has been proposed[90] and is a possible explanation of the phosphoryl bond order uniformity observed in Table 4.7. It is evident from the P-N-C bond angle of 124.7(4) Å, that the geometry of the nitrogen atom is planar rather than pyramidal. This is consistent with the observation that pyramidal nitrogen atom geometry has only been observed in phosphylamidates bearing non-conjugating substituents, such as alkyl groups, at the nitrogen atom.[73] The observed planarity of the OPNHCO fragment (Table 4.9, plane 4) is indicative of extensive Π-electron delocalisation within this fragment. The phenyl ring is twisted with respect to the imide plane by approximately 18.5°, as indicated in Tables 4.9 and 4.10. However, ring twist out of the amide plane appears to be a common property of the N-substituted benzamide structures previously studied, and torsion angles varying between 14 and 32° have been reported.[79] The observed deviation from planarity is probably a consequence of intermolecular ring-ring and/or hydrogen bonding[91] interactions which are operative in the solid state, but are significantly reduced, or even absent in dilute solution. The orientation of the ring with respect to the imide plane is illustrated in Fig. 4.2.

The orientation of the phosphoryl and N-H groups is *syn*-coplanar, as opposed to the *anti*-coplanar orientation of the carbonyl and N-H groups. The mixed imide conformation is thus *'cis-trans'* with the partially opposing phosphoryl and carbonyl dipoles oriented at 127° to one another. This conformational preference parallels that found in symmetrical carboxylic imides where dipole moment studies have shown that imides such as diacetimide (4.8) and N-methyldiformimide (4.9) favour the *cis-trans* orientation over the alternative *cis-cis* and *trans-trans* orientations.[75b,92]

Table 4.9 Coefficients A, B, C, D of the equation to the plane, AX + BY + CZ + D = O, where X, Y, Z are coordinates relative to orthogonal axes. Deviations in Å of individual atoms from planes; root mean square deviations in parentheses.

Plane 1 :	C(11), C(12), C(13), C(14), C(15), C(16)	(0.003)
	0.204; 0.767; 0.608; 5.853	
	P(1) = -0.481	
Plane 2 :	P(1), O(1), O(11), N(1), H(1), C(1), C(11)	(0.046)
	0.050; 0.579; 0.814; 5.471	
	C(12) = 0.416	
Plane 3 :	C(1), C(11), C(12), C(16)	(0.001)
	0.211; 0.764; 0.610; 5.869	
	P(1) = -0.451	
Plane 4 :	P(1), O(1), O(11), N(1), H(1), C(1)	(0.041)
	0.029; 0.585; 0.811; 5.348	
	C(12) = 0.495	

Table 4.10 Angle between normals to least squares planes (as defined in Table 4.9).

Plane 1 - Plane 2	18.31(3)
Plane 1 - Plane 3	0.43(2)
Plane 1 - Plane 4	18.64(3)
Plane 2 - Plane 3	18.33(3)
Plane 2 - Plane 4	1.27(2)
Plane 3 - Plane 4	18.69(3)

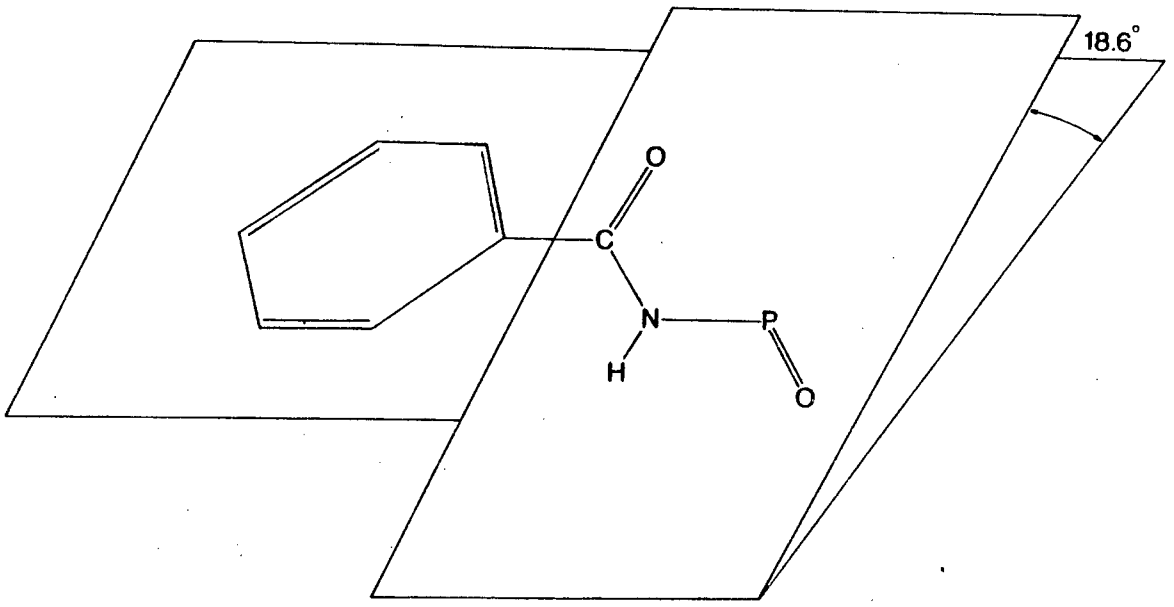
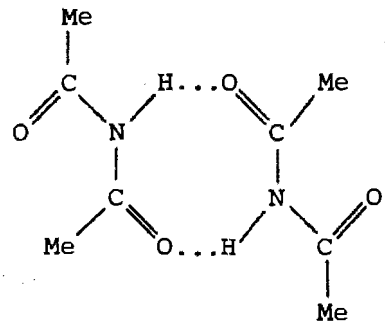
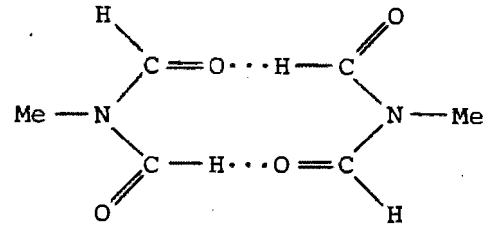


Figure 4.2 The mutual orientation of the ring and mixed imide planes.



(4.8)



(4.9)

It is of interest to note that both the phosphoric and the carboxylic amide conformational preferences (*cis* and *trans* respectively) are retained in the mixed imide system and as such, the intermolecular hydrogen bonding patterns (4.3) and (4.4) are, in principle, both possible. The intermolecular hydrogen bonding pattern is most effectively illustrated in Fig. 4.4 and the various structural parameters associated with it are given in Table 4.11. Pairs of molecules are found to form a dimeric association by two P=O...H-N hydrogen bonds, with the carbonyl group having no involvement whatsoever in the intermolecular association. Spectroscopic evidence for the apparent preference for P=O...H-N over C=O...H-N hydrogen bonding in a variety of secondary N-acyl phosphoramidates has been obtained both in this work (Chapter 3) and elsewhere[93] and suggests a greater stability of the former. In addition, the relative donor abilities of the carbonyl and phosphoryl groups in hydrogen bonding may qualitatively correlate with their solution basicities. In this regard, measurements in strongly acidic media have demonstrated that the CO group of acetophenone is *ca.* 10^4 times less basic than the PO group of diphenylmethylphosphine oxide.[94]

The strength of a hydrogen bond, as measured by the N...O distance, depends upon the acidity of the hydrogen atom involved and thus, upon the nature of the third substituent R' at nitrogen. The N...O distance of 2.815(6) Å observed in the mixed imide (1a) is significantly shorter than the average

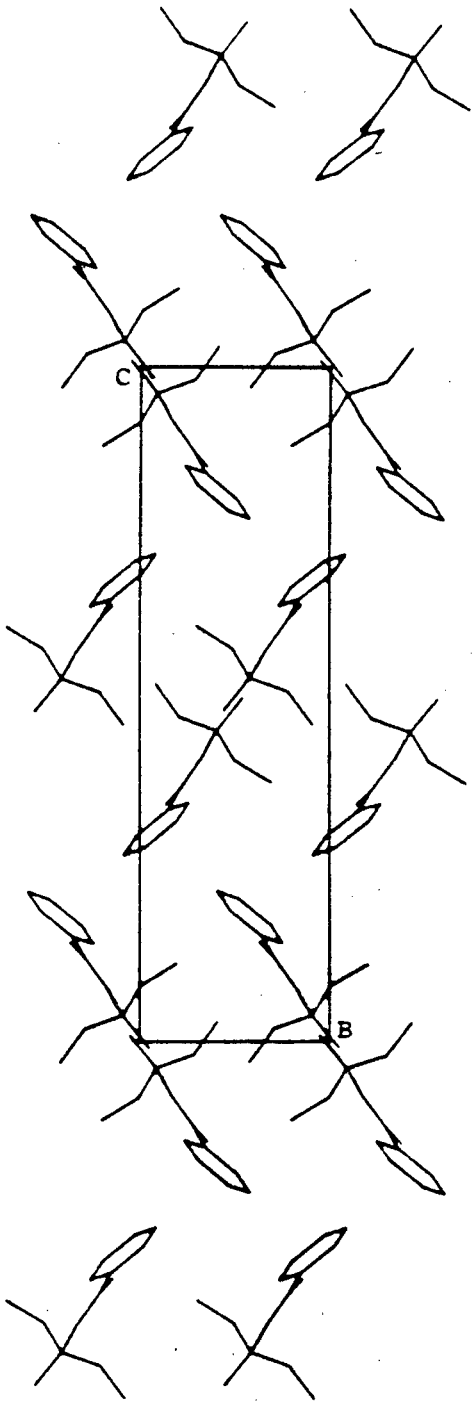


Figure 4.3 **Projection of the crystal packing down the *a* axis.**

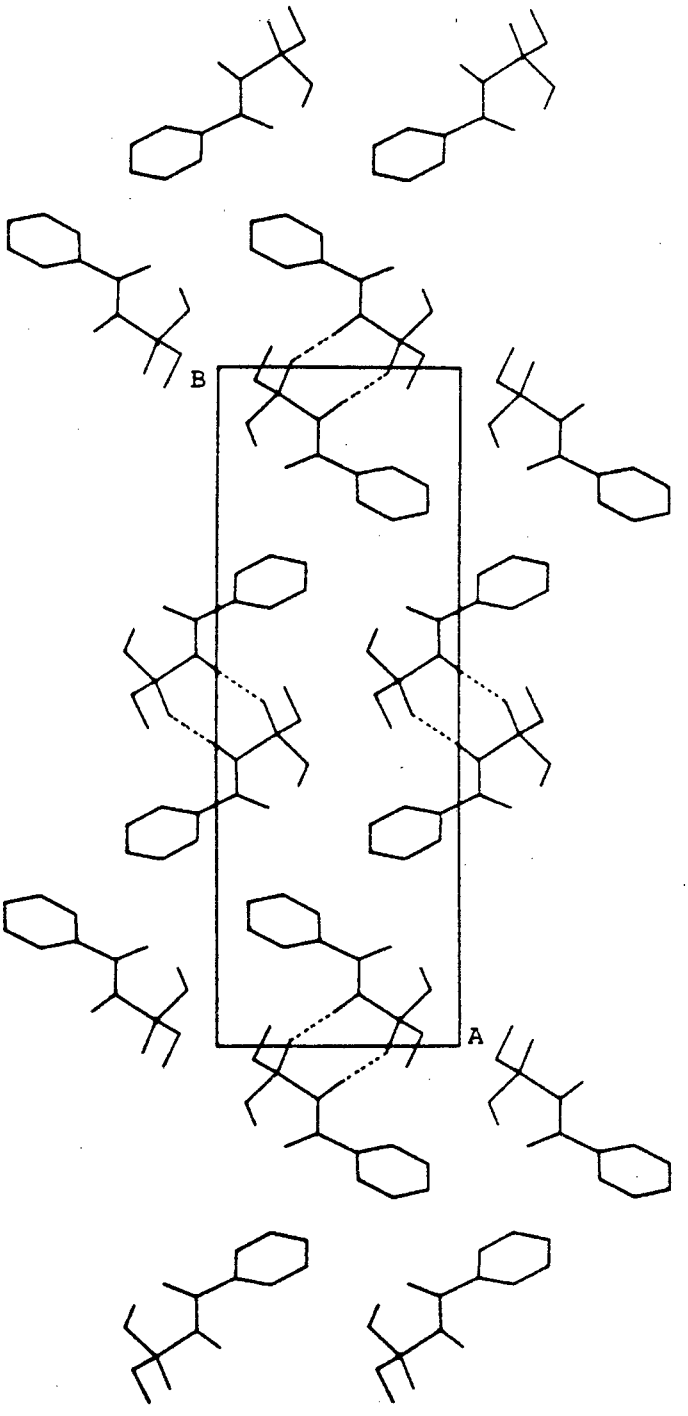


Figure 4.4 Projection of the crystal packing down the *c* axis.

Table 4.11 Hydrogen bonding parameters.

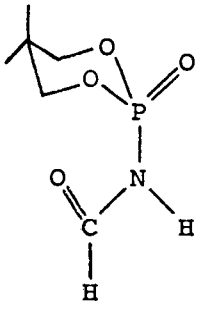
N(1A)....H(1A)	1.001(10) Å (constrained)
H(1A)....O(1B)	1.817(6) Å
N(1A)....O(1B)	2.815(4) Å
N(1A)....H(1A)....O(1B)	174.4(3)°

Table 4.12 Close contacts (< 3.5 Å).

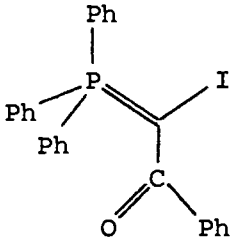
Atoms	Distance, Å	Symmetry operation
P(1A)....O(11A)	2.969	x, y, z
O(1A)....O(1B)	3.243	1-x, -y, 2-z
O(1A)....N(1B)	2.815	1-x, -y, 2-z
C(15A)....O(11B)	3.368	-x, ½-y, -z
O(1A)....C(12B)	3.264	1-x, -y, 2-z
C(7A)....C(12B)	3.397	1-x, -y, 1-z
O(3)....C(13)	3.487	1+x, y, z

value of 2.885(4) Å observed in the series of phosphoramidates $(MeO)_2P(O)NHAr$ (Ar = C_6H_5, 2-Et-C_6H_4, 4-MeO-C_6H_4) and is similar to the value of 2.83(1) Å observed in N-p-nitrophenyldimethylphosphoramidate.[79] Since all the compounds considered exhibit the same dimeric association, the observed variation in the N···O distance clearly reflects hydrogen atom acidity differences.[95]

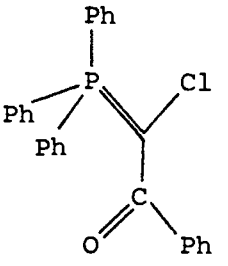
As a result of the planarity of the OPNHCO fragment and its *cis-trans* conformation, the carbonyl oxygen is located directly beneath the tetrahedral face defined by the N1, O2 and O3 atoms, as illustrated in Fig. 4.5. The non-bonding distance of 2.97 Å between the carbonyl oxygen and phosphorus atoms is considerably less than the sum of their van der Waals radii (3.30 Å) and thus constitutes a close contact (Table 4.12). Analogous close contacts between carbonyl oxygen and phosphorus have been observed in the phosphorinane (4.7),[89] in the ylides (4.10)[97a] and (4.11),[97b] and in the phosphonium salts (4.12)[97c] and (4.13):[97d]



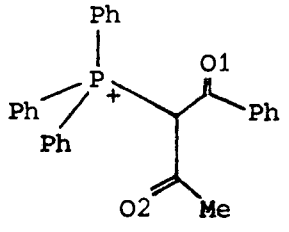
(4.7): 3.00 Å



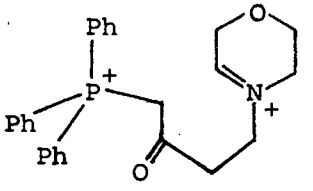
(4.10): 2.773 Å



(4.11): 2.847 Å



(4.12): O1, 2.914 Å
O2, 2.944 A



(4.13): 3.039 Å

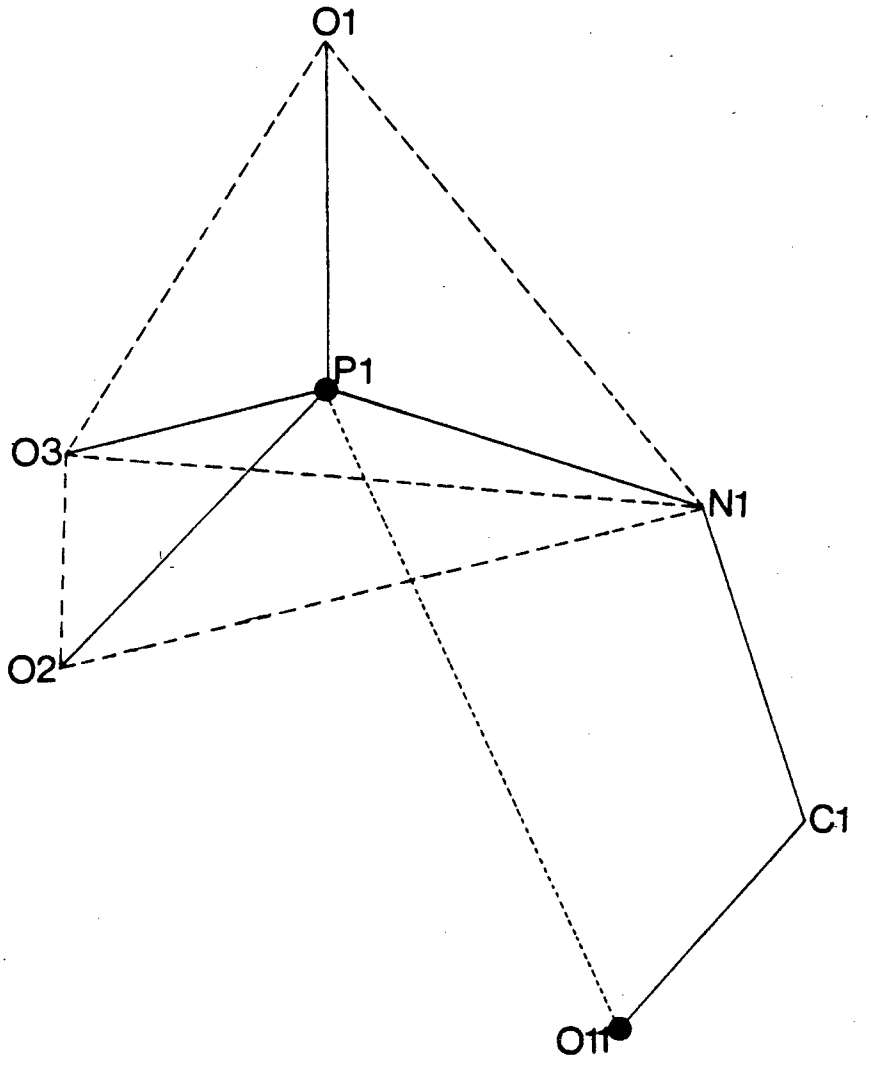
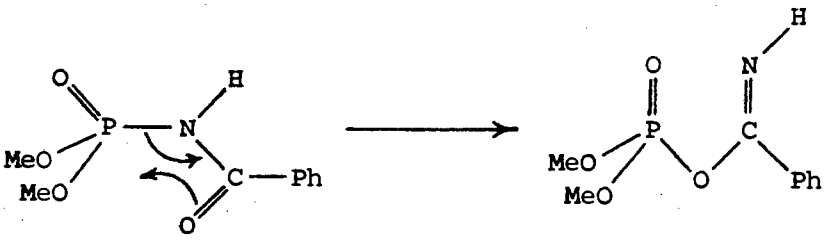


Figure 4.5 The intramolecular close contact between the carbonyl oxygen and phosphorus atoms in (1a).
$d(C{=}O\cdots P^{IV})$ = 2.97 Å.

The most obvious effect of the close contact between the nucleophilic carbonyl oxygen and the electrophilic phosphorus atoms on the structural parameters of the mixed imide, is a significant decrease of the O1-P-N angle from an average value of 111.0° in the series of N-arylphosphoramidates (Table 4.7), to a value of 107.5°. This decrease is, as such, suggestive of a distortion of the phosphorus atom pyramidality. However, it has been shown that when all the angles L_i-P-L_j ($L_{i,j}$ = O1, O2, O3, N; $i \neq j$), as opposed to merely one, are taken into account in the determination of the pyramidal distortion, the angular deviation of the O_3PN tetrahedron of the mixed imide from the average tetrahedron in the series of N-arylphosphoramidates $(MeO)_2P(O)NHAr$, is negligibly small.[79b]

Bimolecular nucleophilic substitution at tetravalent phosphorus involves initial approach of the nucleophile towards either a face or an edge of the tetrahedron. Application of the Structure Correlation Principle to a series of phosphonium ions has recently provided structural evidence[79,98] in support of the earlier stereochemical indication of face approach of a nucleophile towards a phosphonium centre. The secondary interaction observed in the mixed imide may thus be considered as a model of an "early stage" of nucleophilic displacement at a phosphoryl centre, in which the entering nucleophile approaches a face of the tetrahedron. Completion of the nucleophilic substitution reaction alluded to by the C=O...P^{IV} close contact, results in a transfer of the phosphoryl from nitrogen to oxygen as illustrated in eq. 4.1:



[4.1]

This molecular transformation is recognised as corresponding to the isomerisation reaction, for which indirect evidence has been obtained under conditions of electron impact (see Chapter 5). The significance of the $C{=}O\cdots P^{IV}$ secondary interaction is thus two-fold: not only does it provide an illustration of the face approach of an intramolecular nucleophile to a phosphoryl centre, but it also represents the "chemical conception" or first stage of an extremely important, yet rather elusive reaction of N-acyl phosphylamides.

CHAPTER 5

Electron Impact Fragmentation

5.1 INTRODUCTION

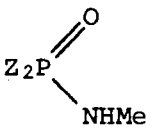
The electron impact-induced fragmentation pathways available to a given system, are largely a function of the site at which the positive charge resides in the molecular ion and are therefore dependent upon the nature of the functional groups within that system. Based on this premise, a certain degree of uniformity in the fragmentation patterns exhibited by members of the same class of compounds can be expected, and is used to great advantage in the analysis of the fragmentation patterns of new systems. In this regard, an element of uniformity is generally introduced into the fragmentation pathways of heteroatom-containing systems, by virtue of the preferential ionisation of the heteroatom non-bonding electrons[99] and resulting similarity in molecular ion structure throughout the system. In the mixed imide system, the ionisation potentials of the oxygen and nitrogen atoms of the $\rangle$P(O)-N(-)-C(O)- moiety (the relative values of which are dependent upon the electronic distribution therein) determine the molecular ion structure and hence the fragmentation pattern. A comparative analysis of the fragmentation behaviour of the mixed imide system and the parent phosphylamide and carboxamide systems was therefore carried out with the aim of firstly, investigating the dynamics and bonding characteristics of the OPNCO functionality and secondly, characterising any novel fragmentations that may arise from an unsymmetrical imide skeleton.[100]

5.2 RESULTS AND DISCUSSION

5.2.1 FRAGMENTATION PATTERNS OF THE PARENT AMIDE SYSTEMS

It has been found that the fragmentation characteristics of a wide variety of secondary and tertiary carboxylic amides are well established, thus partially providing the relevant information for the comparison alluded to

above. In contrast, the paucity of available information on the mass spectrometry of organophosphorus amides necessitated the independent analysis of the fragmentation patterns of the N-methylphosphylamidates (5.1a,b,c):



(5.1)

a, Z = MeO
b, Z = EtO
c, Z = Et

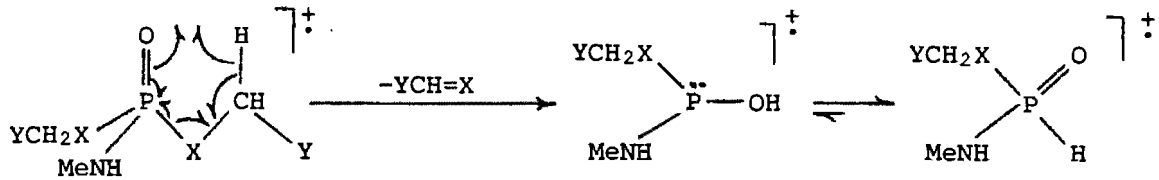
The fragmentation behaviour of amidates (5.1a,b) could be compared with the corresponding primary amides reported by Jakobsen *et al.*[101] and that of the phosphinamide, (5.1c) compared with diethylphosphinic acid and its esters.[102] The primary products formed in the fragmentation of substrates (5.1) are listed in Table 5.1; the primary products give rise to subsequent fragments which have been omitted from Table 5.1 for the sake of clarity. The generalised fragmentation pattern of the phosphylamide system (5.1) is presented in Scheme 5.1; metastable-supported pathways are designated by an asterisk.[103]

The molecular ions derived from substrates (5.1) are capable of undergoing P-N bond cleavage by liberating a disubstituted phosphacyl radical and methylene iminium ion (pathway a). In this respect, N-methylphosphylamides parallel aliphatic N-methylcarboxamides, the mass spectra of which also typically contain a prominent peak at m/e 30.[104] The second pathway common to all substrates (5.1), is probable homolytic cleavage of the P-X bond (pathway b) resulting in the formation of a phosphacylium ion, which is additionally stabilised by the adjacent nitrogen atom (m/e 106, 108, 122). A third route available to system (5.1) is via five-centred hydrogen shift and elimination of a neutral molecule of aldehyde or ethylene (pathway c, eq. 5.1) and methylene imine (pathway d, eq. 5.2):

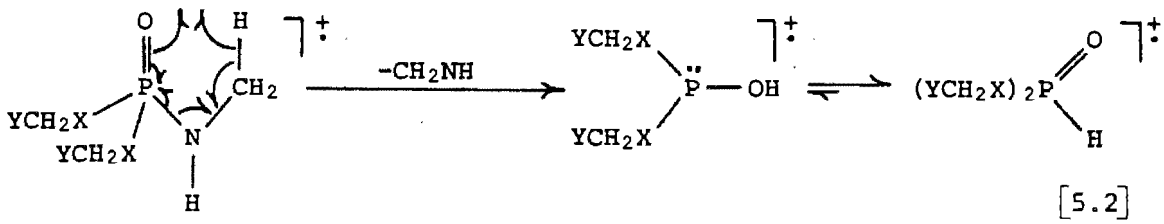
Table 5.1 Selected ions in the mass spectra of N-methyl dialkylphosphoramidates and phosphinamidates.

		Substrate		
		(5.1a)	(5.1b)	(5.1c)
Pathway[a]	m/e	Relative intensity (%)		
a	30	98	96	34
b	106	-	-	100
	108	66	-	-
	122	-	16	-
c	107	-	-	28
	109	100	-	-
	123	-	16	-
d	106	-	-	100
	110	96	-	-
	138	-	24	-
e	139	-	31	-
f	140	-	14	-

[a] Scheme 5.1



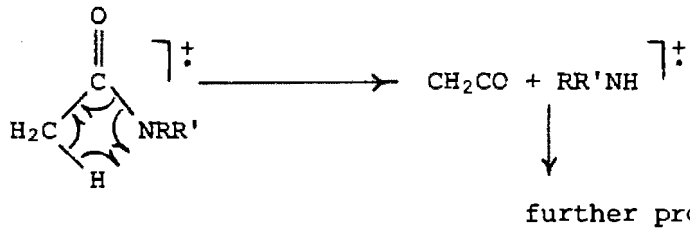
[5.1]



[5.2]

The remaining two fragmentation pathways (pathways e, f) are specific to the diethyl ester (5.1b). The presence of a β-carbon atom in the ester function complicates the mass spectrum of this substrate in relation to (5.1a,c). The additional fragmentations introduced by the P(O)OEt function in the molecular ion are well established for ethyl esters of phosphoric acid.[101,105,106] Loss of ethylene (pathway e) occurs via the typical McLafferty rearrangement[107] to yield the phosphoramidate monoester radical ion m/e 139. Loss of vinyl radical, $C_2H_3^{\cdot}$ (pathway f) to yield the quasi-phosphonium ion m/e 140, involves a double hydrogen rearrangement.[106] It is interesting to note that the apparently stable phosphorylium ion $MeNH\text{-}\overset{+}{P}(O)OH$ (m/e 94) which is the base peak in the MS of (5.1b), is not formed by fragmentation of the dimethyl ester (5.1a) radical ion. This is consistent with the observation that all fragmentation routes of (5.1b) leading to the formation of this ion involve the abstraction of two-carbon species from the corresponding precursor ions, e.g. m/e 140 $\xrightarrow{-EtOH}$ m/e 94 or m/e 139 $\xrightarrow{-EtO^{\cdot}}$ m/e 94. In conclusion, the mass spectra of amides (5.1) indicate that the radical ion produced from the system $Z_2P(O)NHR$ has a complex decomposition pattern, dependent on both the nature of the group Z and the amide function, with fragmentations commonly accompanied by hydrogen and skeletal rearrangements.

The mixed imides (1a-g) under investigation, can be considered as benzamide and acetamide derivatives, structurally modified at the nitrogen atom. The two major fragmentation pathways available to benzamide derivatives are acyl-nitrogen fission yielding benzoylium ion (m/e 105, typically the base peak) and expulsion of $H^{\cdot}$ from the aromatic ring to yield a commonly prominent (M-1) species.[108] Acetamide derivatives undergo analogous acyl-nitrogen cleavage to yield acetylium ion (m/e 43); their second important fragmentation pathway involves hydrogen migration from the acetyl methyl to nitrogen and the resultant expulsion of a neutral molecule of ketene from the molecular ion (eq. 5.3):[109]



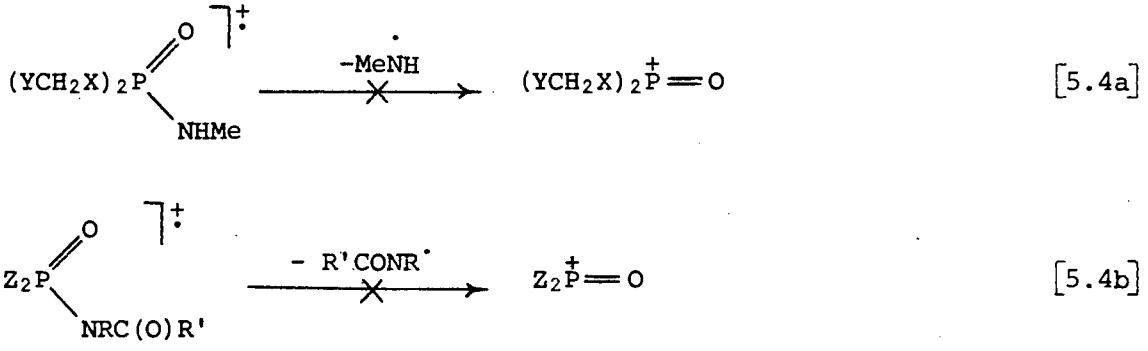
[5.3]

A knowledge of the fragmentation characteristics discussed above, facilitates the analysis of the mixed imide fragmentation from both a phosphylamide and carboxamide point of view.

5.2.2 FRAGMENTATION PATTERNS OF THE MIXED IMIDES

The main ions observed in the mass spectra of the N-benzoyl (1a,b,e) and N-acetyl (1c,d,f,g) derivatives are listed in Tables 5.2 and 5.3 respectively, and the fragmentation patterns responsible for the formation of these ions are presented in Schemes 5.2 — 5.8. Analysis of the general fragmentation behaviour of the mixed imides indicates a partial retention of the fragmentation characteristics of their parent amides, as well as the appearance of novel fragmentation pathways. Of the three N-benzoyl derivatives studied, only (1a) shows the loss of an aromatic hydrogen to yield the (M-1) ion

characteristic of substituted benzamides. However, all three undergo benzoyl-nitrogen fission, to produce the benzoylium ion (m/e 105; Scheme 5.2, pathway b; Schemes 5.3, 5.4, pathways a). Similarly, acyl-nitrogen cleavage yielding acetylium ion (m/e 43; Scheme 5.5 - 5.8, pathways a) is observed for all the N-acetyl derivatives. It is of interest to note that the analogous fission of the phosphacyl-nitrogen linkage is not observed in either the phosphylamide system (5.1) or the mixed imide system (1) (eqs. 5.4a,b).



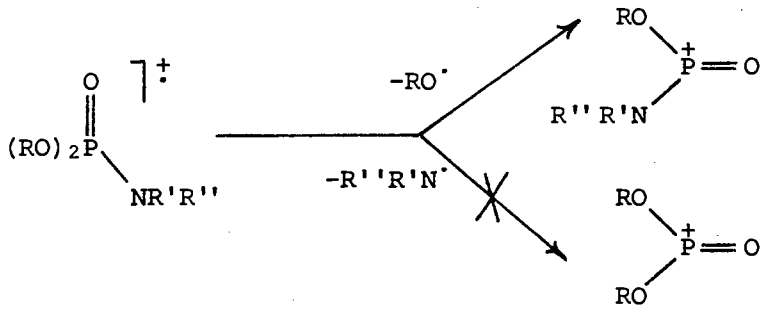
[5.4a]

[5.4b]

Jakobsen *et al.*[101] have similarly reported the absence of P-N fission of the molecular ion of primary dialkylphosphoramidates $(RO)_2P(O)NH_2$ (R = Me, Et) and have found that since fragmentations associated with the ester function prevail, all the major ionic fragments have an intact P-N linkage. As indicated in Schemes 5.2 and 5.5, the dimethylphosphorylium ions apparent in the MS of derivatives (1a) and (1c), do not originate from the molecular ion itself, but rather emanate from subsequent fragmentations of the primary products.

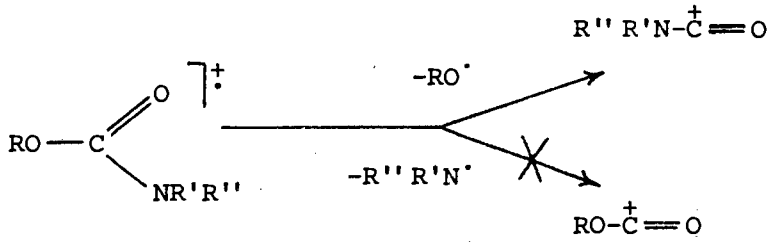
Phosphacylium ions ($Z_2\overset{+}{P}O$) are apparently much less stable than their carboxyacylium ion analogues.[110] However, if Z is bound to phosphorus via a heteroatom (O or N), additional stabilisation is gained by charge delocalisation due to $d_\Pi - p_\Pi$ overlap. One contributory factor to the apparent stability of the P-N bond in the dialkylphosphoramidates, may thus be the

greater ability of a nitrogen- rather than oxygen-bonding substituent to stabilise the incipient positive charge at phosphorus (eq. 5.5);



[5.5]

Substituted carbamates RO-C(O)NR'R'' have been found to exhibit an analogous fragmentation preference,[113] with loss of alkoxy radical constituting a major fragmentation pathway (eq. 5.6):

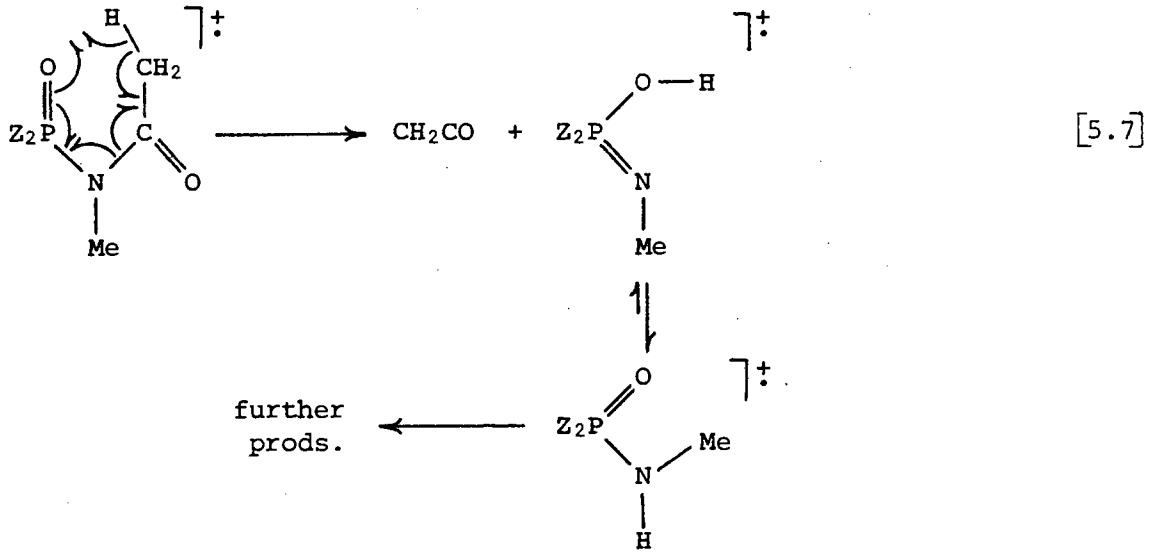


[5.6]

The relative abundance of a given ion is, however, not only a function of its stability, but also depends upon the number of fragmentation pathways from which it can arise and hence, upon the site of the positive charge in the precursor ion. All mass spectra reported in Tables 5.1 - 5.8 were recorded at an ionising energy of 70 eV, which is well in excess of the ionisation potentials of the oxygen and nitrogen atoms of an amide system. It must therefore be assumed that two types of molecular ion of the parent amides are formed, depending on whether electron removal is from a lone pair on oxygen (phosphacyl or carbonyl) or nitrogen; each subsequently fragments via certain favoured pathways.

In this regard, the mixed imide system is complicated by the presence of three likely sites for electron ejection. However, the observed fragmentation

preferences indicate that in the molecular ions derived from (1), localisation of the radical cationic character is in the N-C(O) rather than N-P(O) function. Decomposition of the molecular ions of the N-benzoyl derivatives via benzoylium ion (base peak at 70 eV) formation and via loss of hydrogen and phenyl radicals, arises from fragmentation of the PhC(O)N moiety. Similarly, involvement of the MeC(O)N moiety in the fragmentation of the N-acetyl derivatives is indicated by the presence of acetylium ion and fragmentation products arising from the initial loss of ketene from the molecular ion. Loss of ketene from the mixed imide system, is possibly facilitated by participation of the phosphacyl group in a six-centre hydrogen migration (eq. 5.7) and, as such, is more favourable than the analogous four-centre elimination from simple acetamides[109] (eq. 5.3):

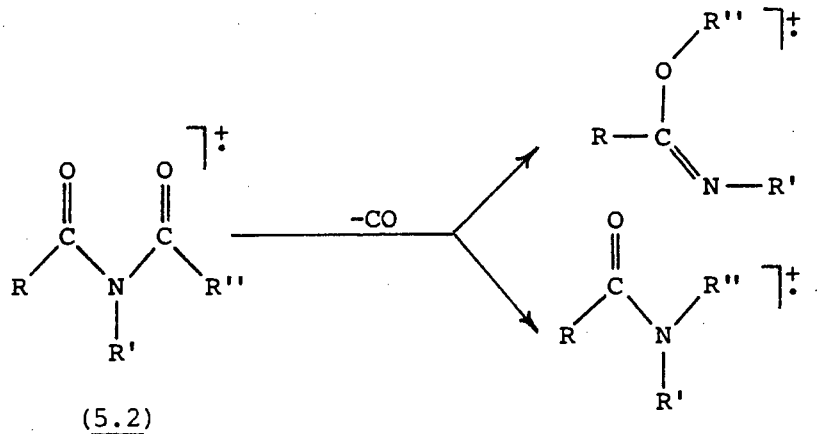


[5.7]

Loss of ketene from (1c,d,f) thus gives rise to radical ions that are identical to the molecular ions derived from (5.1a), (5.1b) and (5.1c) respectively, which subsequently fragment via the pathways suggested in Scheme 5.1.

A fragmentation pathway exhibited by the N-benzoyl derivatives (1a) and (1e), is the expulsion of carbon monoxide from the molecular ion. This type of

fragmentation is characteristic of carboxylic imides and is accompanied by migration of the substituent R'' to either the oxygen or nitrogen atom (eq. 5.8):[114]

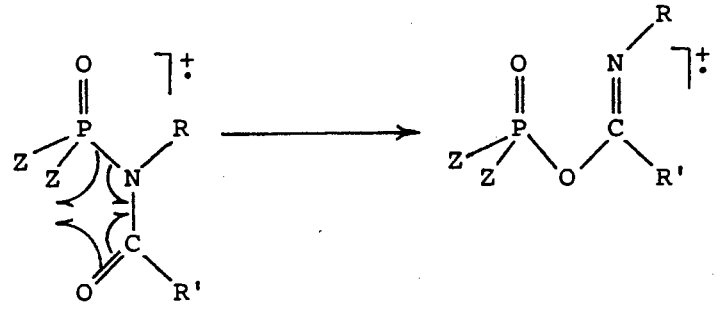


[5.8]

(5.2)

Whilst phenyl migration to nitrogen with loss of CO is observed for (1a,e), no analogous methyl migration to either phosphacyl oxygen or nitrogen is observed for the N-acetyl derivatives (1c,d,f,g).

Besides fragmentation to yield acylium ion, a second pathway common to all the mixed imide molecular ions, is rearrangement to the corresponding O-phosphyl benz- or acetimidates (5.3) (eq. 5.9):

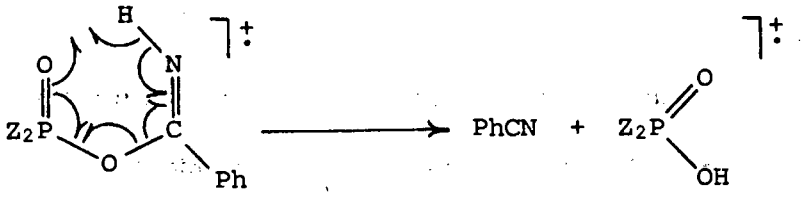


[5.9]

(1) (5.3)

The isomeric radical ion gives rise to new fragmentation patterns, as illustrated in Schemes 5.2 - 5.8. All fragmentations of (5.3) involve cleavage of the C-O bond and may be accompanied by hydrogen migration. Dialkylphosphyl radical ($Z_2PO_2^{\bullet}$) is readily lost yielding N-protonated or N-methylated nitrilium ion $R'C \equiv \overset{+}{N}R$ (R' = Ph, Me; R = H, Me). The

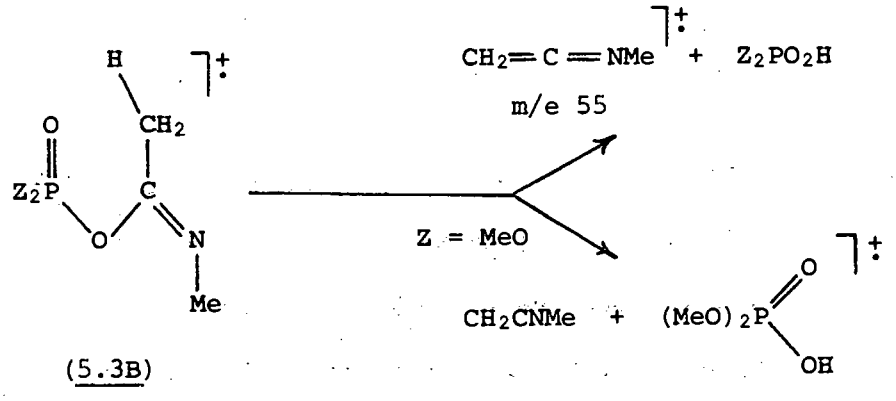
benzimidate radical ions (5.3A) derived from the secondary N-benzoyl compounds (1a,b) undergo benzonitrile elimination via hydrogen transfer to phosphoryl oxygen, to yield dialkylphosphate radical ion (eq. 5.10):



[5.10]

(5.3A)

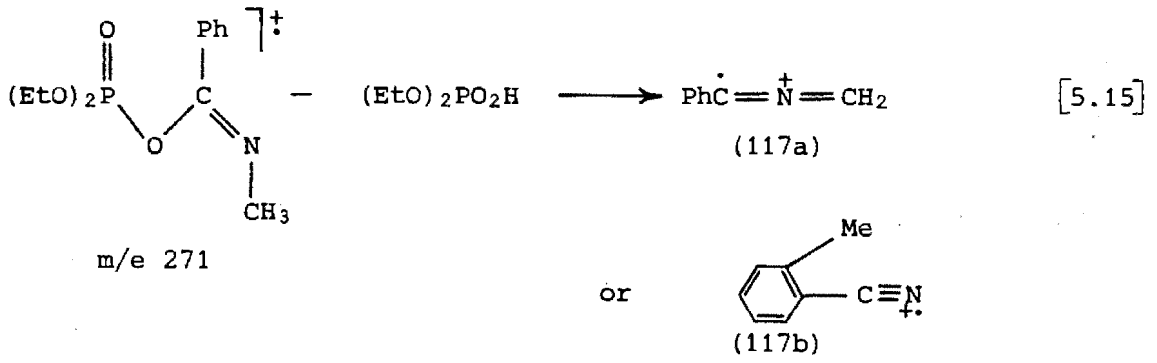
The acetimidate radical ions (5.3B) derived from the N-acetyl compounds (1c,d,f,g) undergo C-O fission accompanied by H-transfer from the C-methyl group to phosphacyl oxygen, producing a ketenimine radical ion (m/e 55; eq. 5.11); the elimination mechanism is analogous to that of ketene loss from the mixed imide precursor (eq. 5.7). The highly delocalised nature of the acetimidate radical ion derived from (1c), is indicated by the formation of dimethylphosphate radical ion via loss of a neutral molecule of ketenimine:



[5.11]

(5.3B)

An interesting and prominent fragmentation of two of the acetimidate radical ions (5.3B) involves C-O fission accompanied by double hydrogen transfer, to give the corresponding quasiphosphonium ion, as illustrated in Schemes 5.5 and 5.7 (eq. 5.12):

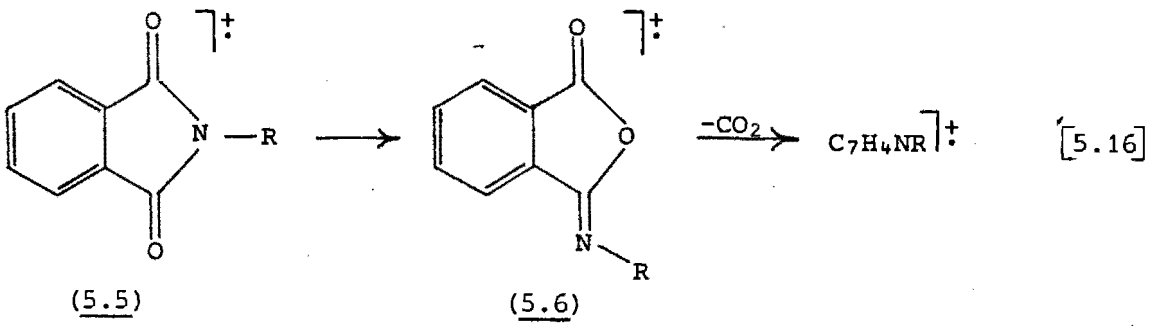


[5.15]

The apparently facile electron impact-induced N → O phosphyl migration occurring in the mixed imides, prompted an investigation into the general applicability of migrations in related systems. In this regard, the observations made by Bentley *et al.*[116] concerning four-centre Π-system rearrangements of the general type $[A=B-C-D]^{\ddagger} \longrightarrow [D-A-B=C]^{\ddagger}$ are relevant. It has been found that migration of a p_{Π} orbital-containing group D can occur under the following conditions: (i) when A is oxygen, C must be nitrogen; (ii) when A is sulfur, C can be nitrogen or oxygen, (iii) B can be carbon, phosphorus or nitrogen.[116c] N-Aryl carboxylic amides have been found to undergo electron impact-induced aryl migrations (A = O, C = N, D = aryl).[117] In contrast, ions derived from N → O aryl migration are absent in the mass spectra of N-phenyl dimethylphosphoramidate and related N-aryl phosphoric amides,[105a] thus indicating that such migrations are less favoured in phosphoric than carboxylic amide systems. However, since the extent to which a skeletal rearrangement operates is partly governed by the ease of competing fragmentations, it is possible that alternative cleavage reactions mask the N → O aryl migration reaction in phosphoric amides.

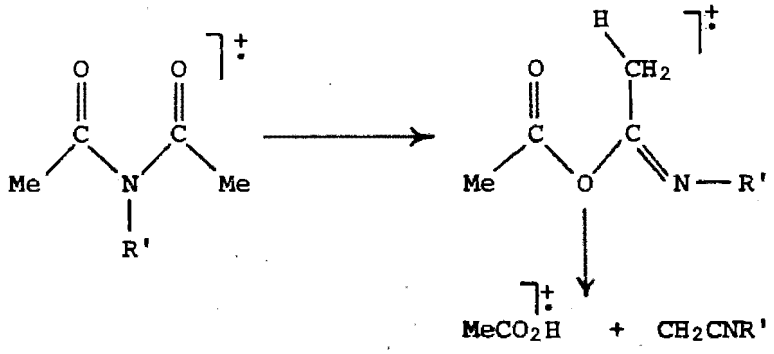
A major fragmentation pathway available to cyclic imides, such as N-substituted phthalimides (5.5) and maleimides, involves expulsion of carbon dioxide from the molecular ion. This reaction has been shown to proceed via electron impact-induced aroyl migration, to yield the corresponding

isoimide radical ion (5.6), followed by loss of CO_2 (eq. 5.16):[116b]



(5.5) (5.6) [5.16]

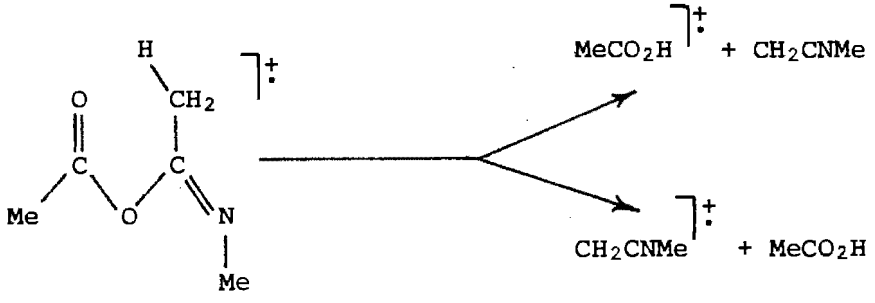
Acyl migration in acyclic imides is more rare, as a result of masking by the favourable competitive N-acyl cleavage reactions. The operation of an aroyl migration pathway, albeit minor, in the imide $4-NO_2-C_6H_4C(O)-NMe-C(O)CF_3$ is evidenced by the appearance of $MeN^{+}\equiv C-CF_3$ ion (m/e 110) in the mass spectrum.[116a] In their work on the mass spectra of substituted carboxylic imides $RC(O)-NR'-C(O)R''$ (5.2), Nolde *et al.*[114] exclusively discuss the major fragmentations such as CO loss, simple N-acyl cleavage and ketene loss (R or R'' = Me), without addressing the question of possible isomerisation. However, careful examination of the reported spectra,[114] reveals the presence of acetic acid radical ion (m/e 60) in the mass spectra of some of the diacetimide derivatives (5.2; R = R'' = Me). The formation of this ion is best explained by imide→O-acetyl imidate rearrangement prior to fragmentation (eq. 5.17):



[5.17]

The above observation warranted the analysis of the fragmentation patterns of four substituted imides (5.2a-d), paying particular attention to fragments

that may be derived from initial substrate isomerisation. N-Methyldiacetimide (5.2a; R = R' = R'' = Me; reported previously by Nolde *et al.*[114]) was found to give rise to both acetic acid (m/e 60) and the ketenimine radical ion $CH_2CNMe]^{+\cdot}$ (m/e 55), also present in the previously reported spectrum.[114] The highly delocalised imidate is thus capable of the same type of dual fragmentation (eq. 5.18) observed for (5.3B) (eq. 5.11):

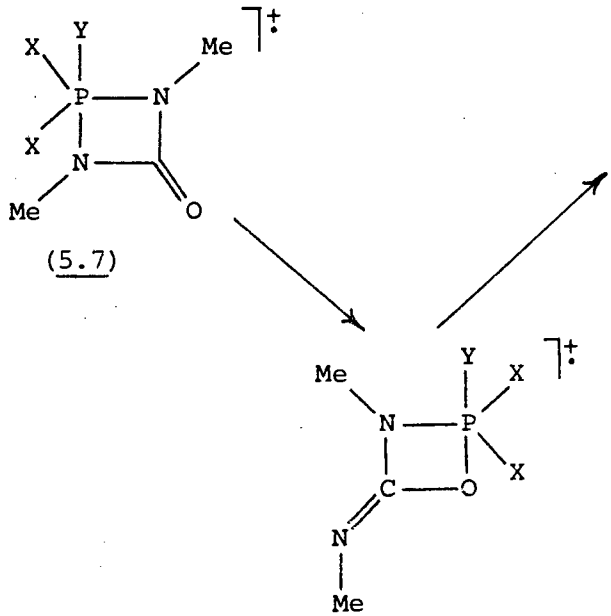


[5.18]

N-Methylacetbenzimide (5.2b; R = Ph, R' = R'' = Me) fragments to yield both acetic (m/e 60) and benzoic acid (m/e 122) radical ions. The greater relative abundance of the latter (8% vs. 3% of the base peak) implies that although both acetyl and benzoyl groups are capable of migrating, aroyl migration is preferred.[118] In contrast, there is no evidence of benzoic acid radical ion in the mass spectra of either dibenzimide (5.2c; R = R'' = Ph; R' = H) or N-methyldibenzimide (5.2d; R = R'' = Ph, R' = Me). However, it is likely that the traces of protonated and methylated benzonitrilium ion $PhC{\equiv}\overset{+}{N}R'$ (R' = H, Me) observed in the mass spectra of (5.2c) and (5.2d) respectively, arise from loss of $PhCO_2^{\cdot}$ from the corresponding O-benzoyl benzimidate.

The competitiveness of a four-centre rearrangement in the system $[A{=}B-C-D]^{+\cdot}$ with other fragmentation pathways, depends upon the energy requirement of the migration process, which is, in turn, related to the nature of the migrating group D and the skeleton $A{=}B-C$. The migration of a P^{IV} or P^{V} group within the $O{=}C-N$ moiety of both acyclic and cyclic systems is certainly competitive with other processes such as N-acyl cleavage, as

indicated by firstly, the relatively high abundance of ions derived from rearrangement of the mixed imides (1a-g) (49 - 100% of the base peak) and secondly, the observed fragmentation preference of several substituted N,N'-dimethyl-1,2,4-phosphadiazetidin-3-ones (5.7), via initial P^V migration (eq. 5.19):[119]



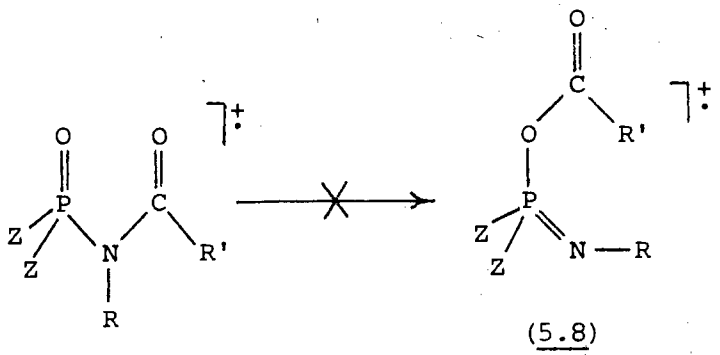
$X_2(Y)P{=}O$]$^{+\cdot}$

and

$MeN{=}C{=}N{-}Me$]$^{+\cdot}$ [5.19]

On the other hand, although carboxyacyl migration within the O=C—N moiety is a competitive reaction of certain cyclic imides (eq. 5.16), the relatively low abundance of the ions derived from initial isomerisation of the acyclic derivatives (5.2a-d, <10% of the base peak) indicates that other fragmentations, notably N-acyl fission, are preferred in such systems.

The dependence of the migration process upon the nature of the A=B—C backbone can be illustrated by considering the changes effected by replacement of the carboxamide skeleton by its phosphylamide analogue (O=P—N). As discussed above, there is no evidence for electron impact-induced N → O aryl migration in N-aryl phosphoramidates. Similarly, the ions present in the mass spectra of the N-acyl phosphylamidates (1a-g) do not suggest any prior N → O carboxyacyl (acetyl or benzoyl) migration to yield the corresponding O-acyl phosphylimidates (5.8):

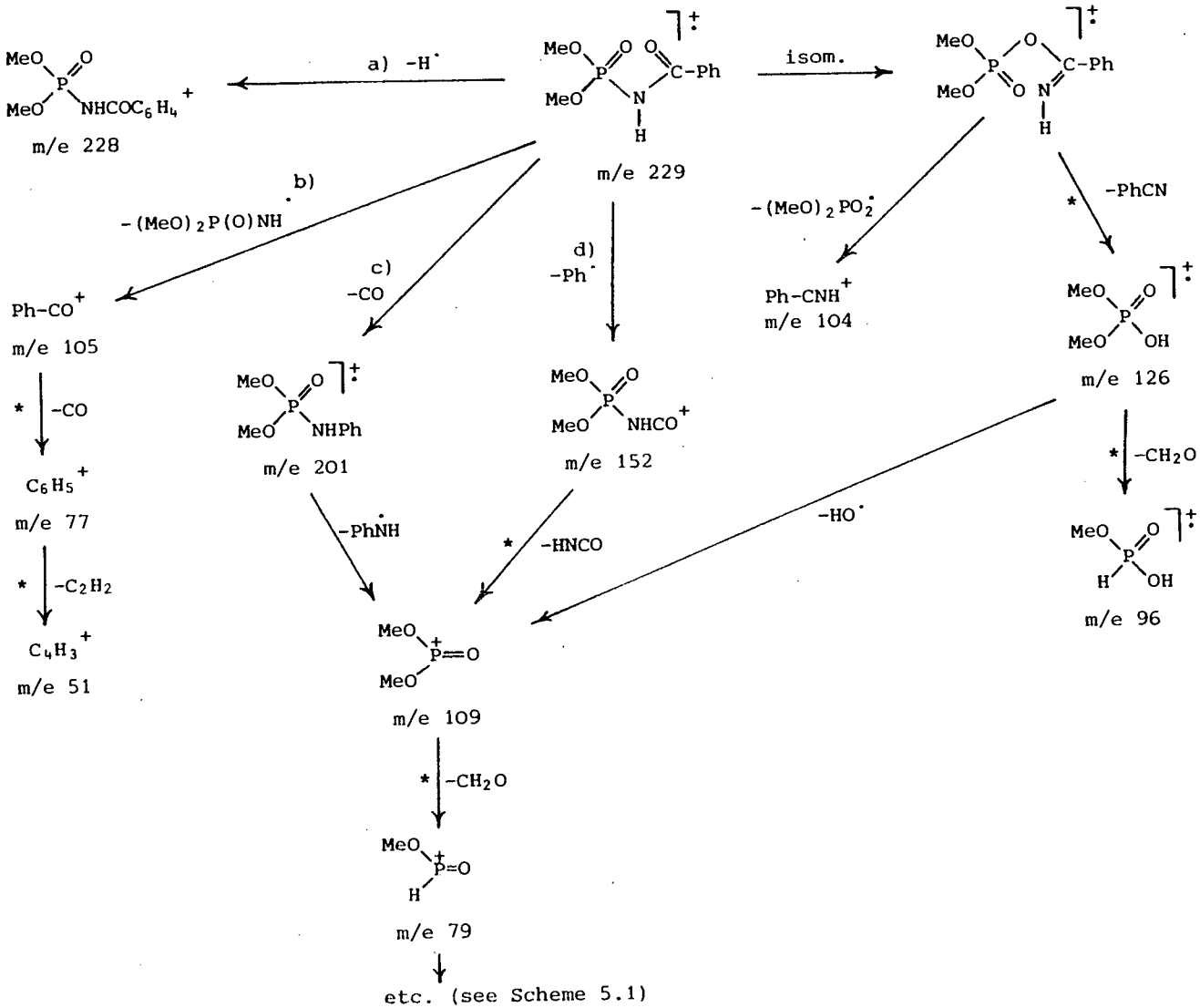


(1) (5.8) [5.20]

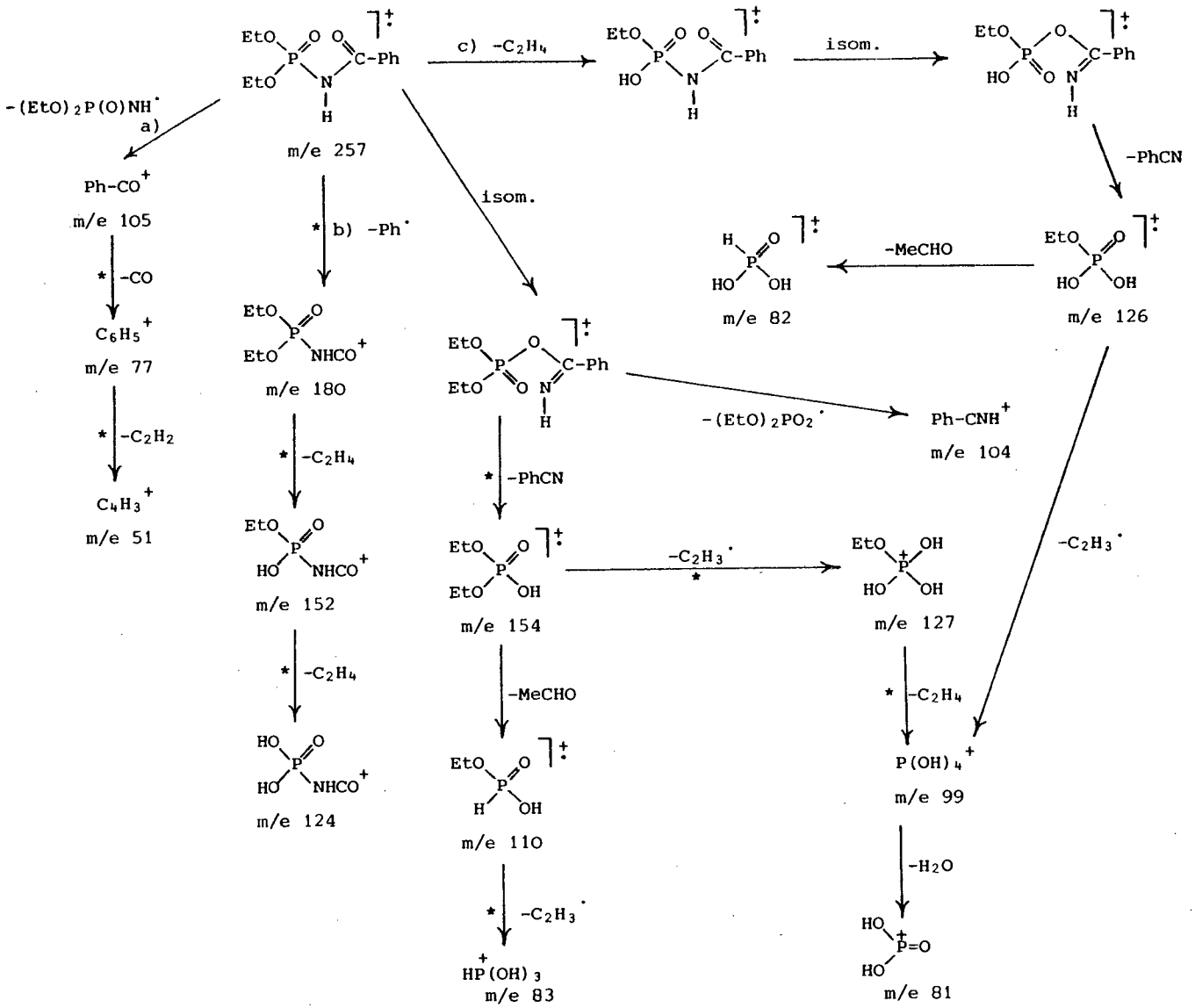
Finally, the absence of dialkylphosphate radical ion/s and ions containing multiple phosphorus-nitrogen bonds in the mass spectra of the symmetrical phosphoric imides $(RO)_2P(O)-NMe-P(O)(OR')_2$ (5.9; a, R = Et, R' = Me; b, R = R' = Et) indicates that phosphoryl migration, which is so facile over the O=C—N backbone, is apparently disfavoured over the O=P—N backbone. According to the generalised migration rules[116c] discussed above (p. 90), N→O migration of an appropriate group D can, in principle, occur in the phosphylamide system O=P—N—D (A = O, B = P, C = N). However, the observations on the phosphylamide systems described above, warrant a modification of the rules to exclude the O=P—N skeleton. The migration process, or lack thereof, therefore constitutes a major difference in the electron impact fragmentation behaviour of carboxamide and phosphylamide systems. The tendency for the mixed imides (1) to undergo N → O phosphyl migration as opposed to N → O carboxyacyl migration, reveals complete retention of this aspect of the fragmentation behaviour of both parent amide systems in the mixed system.

The pronounced difference in the migration abilities can be attributed to a variety of factors; although the bonding characteristics of the oxygen atom in the carbonyl and phosphyl groups are certainly different, one can speculate on the steric nature of this behaviour. In the coplanar carboxamide system, large groups at the nitrogen atom tend to locate themselves

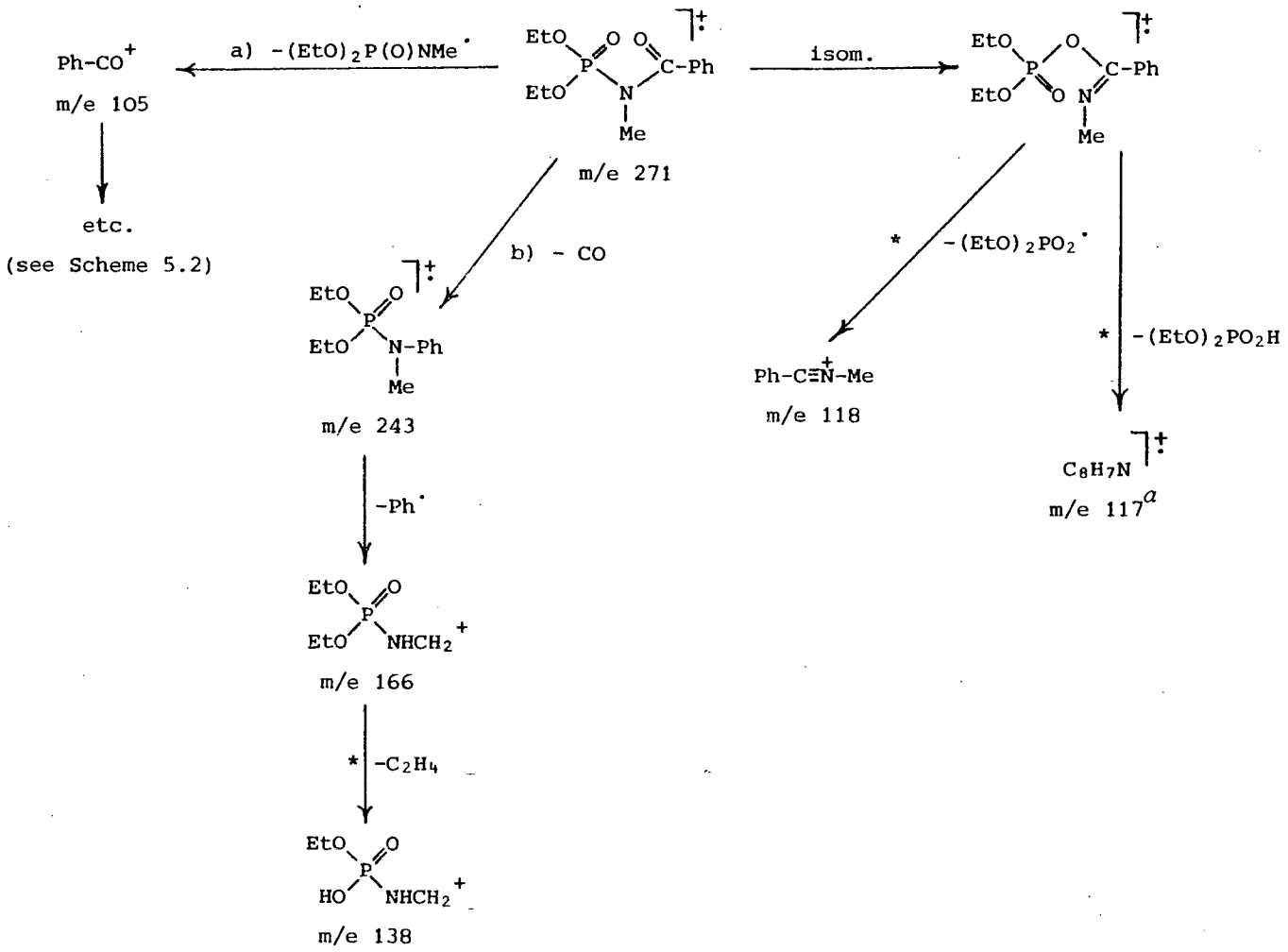
Scheme 5.2


a) -H·
isom.
m/e 228
m/e 229
b)
-(MeO)2P(O)NH·
c)
-CO
d)
-Ph·
-(MeO)2PO2·
* -PhCN
Ph-CO+
m/e 105
Ph-CNH+
m/e 104
m/e 126
* -CO
C6H5+
m/e 77
* -C2H2
C4H3+
m/e 51
m/e 201
m/e 152
-PhNH·
* -HNCO
-HO·
* -CH2O
m/e 109
* -CH2O
m/e 79
m/e 96
etc. (see Scheme 5.1)

Scheme 5.3


m/e 257
a) -(EtO)2P(O)NH·
Ph-CO+
m/e 105
* -CO
C6H5+
m/e 77
* -C2H2
C4H3+
m/e 51
* b) -Ph·
m/e 180
* -C2H4
m/e 152
* -C2H4
m/e 124
c) -C2H4
isom.
isom.
-PhCN
m/e 126
-MeCHO
m/e 82
-(EtO)2PO2·
Ph-CNH+
m/e 104
* -PhCN
m/e 154
-C2H3·
*
m/e 127
-MeCHO
m/e 110
* -C2H3·
HP(OH)3+
m/e 83
* -C2H4
P(OH)4+
m/e 99
-H2O
m/e 81
-C2H3·

Scheme 5.4

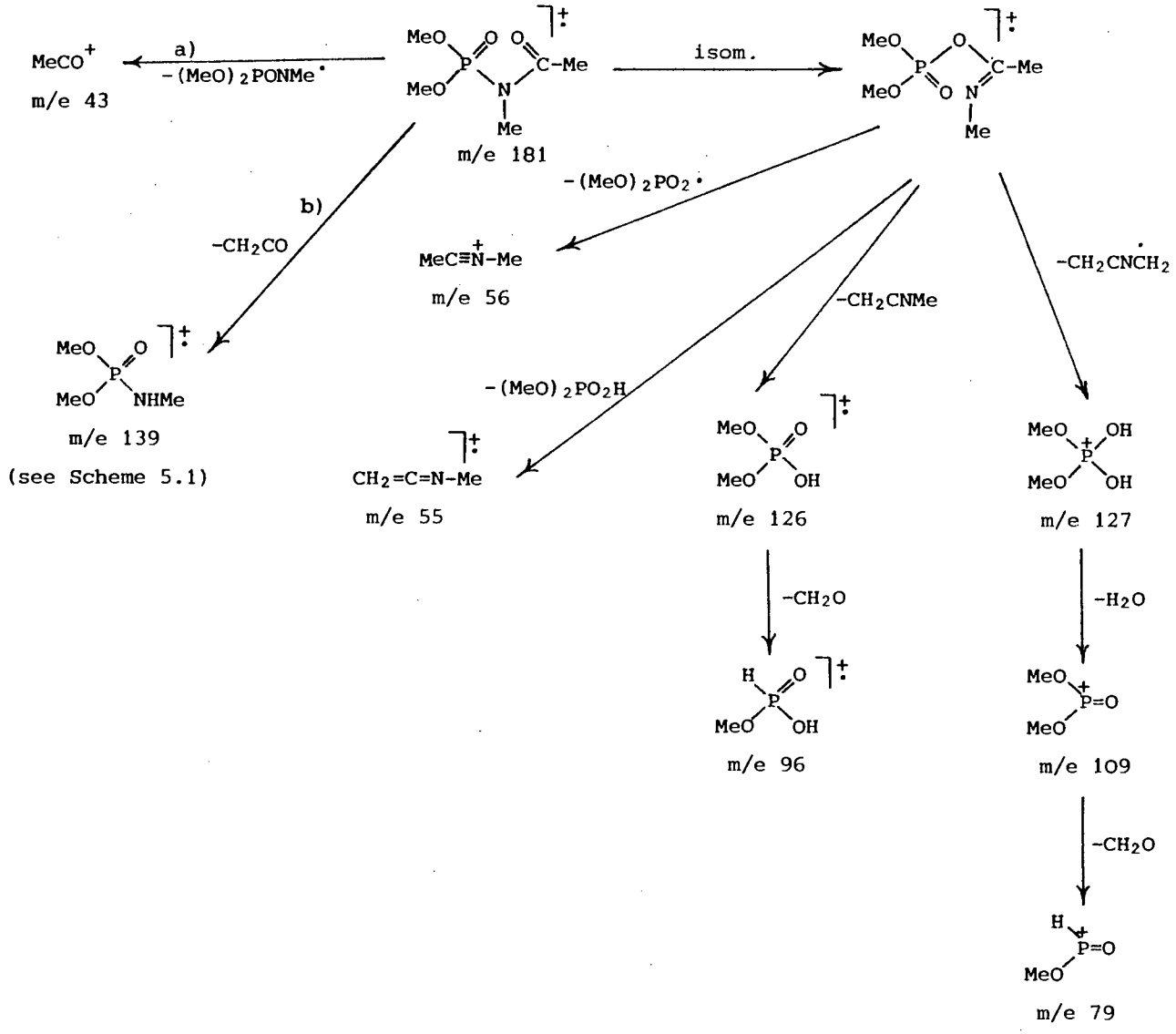


[a]See text for probable structure of this radical ion.

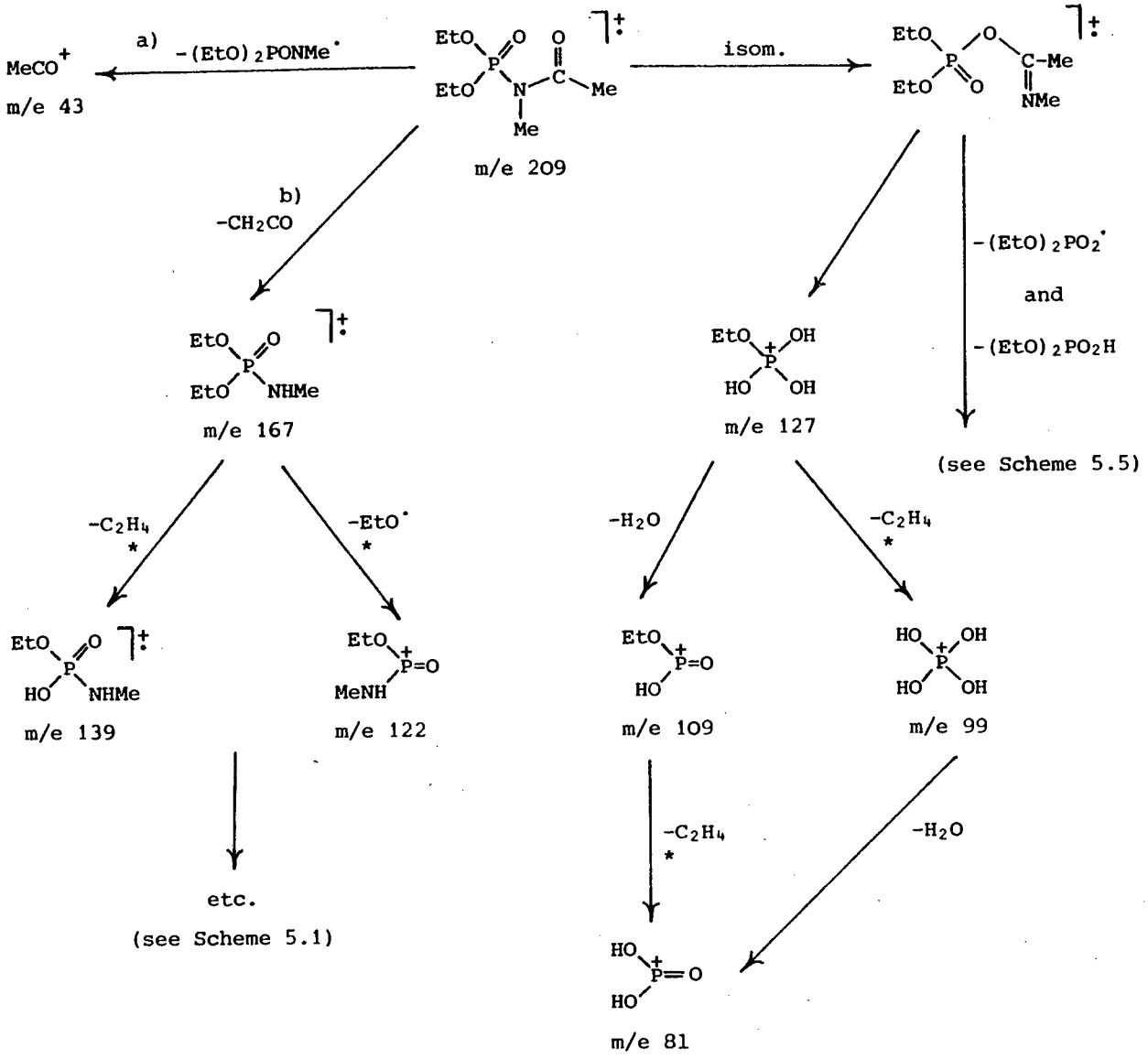
Table 5.3 Main ions in the mass spectra of the N-acetyl N-methyl phosphylamidates.

	Substrate			
	(1c)	(1d)	(1f)	(1g)
MW	181	209	177	179
m/e	Relative Intensity (%)			
Mol. ion	2	1	2	2
43	44	30	28	50
55	95	46	76	100
56	25	20	100	34
77	-	-	16	-
78	-	-	51	-
81	-	-	-	14
96	11	-	-	-
99	-	100	-	-
105	-	-	24	-
106	-	-	19	-
107	-	-	40	11
109	100	15	-	-
122	-	8	-	-
123	-	6	7	-
126	14	-	-	-
127	18	67	-	-
135	-	-	6	-
136	-	-	-	98
137	-	-	-	74
138	61	7	-	-
139	86	16	-	-
148	-	-	29	-
167	-	9	-	-

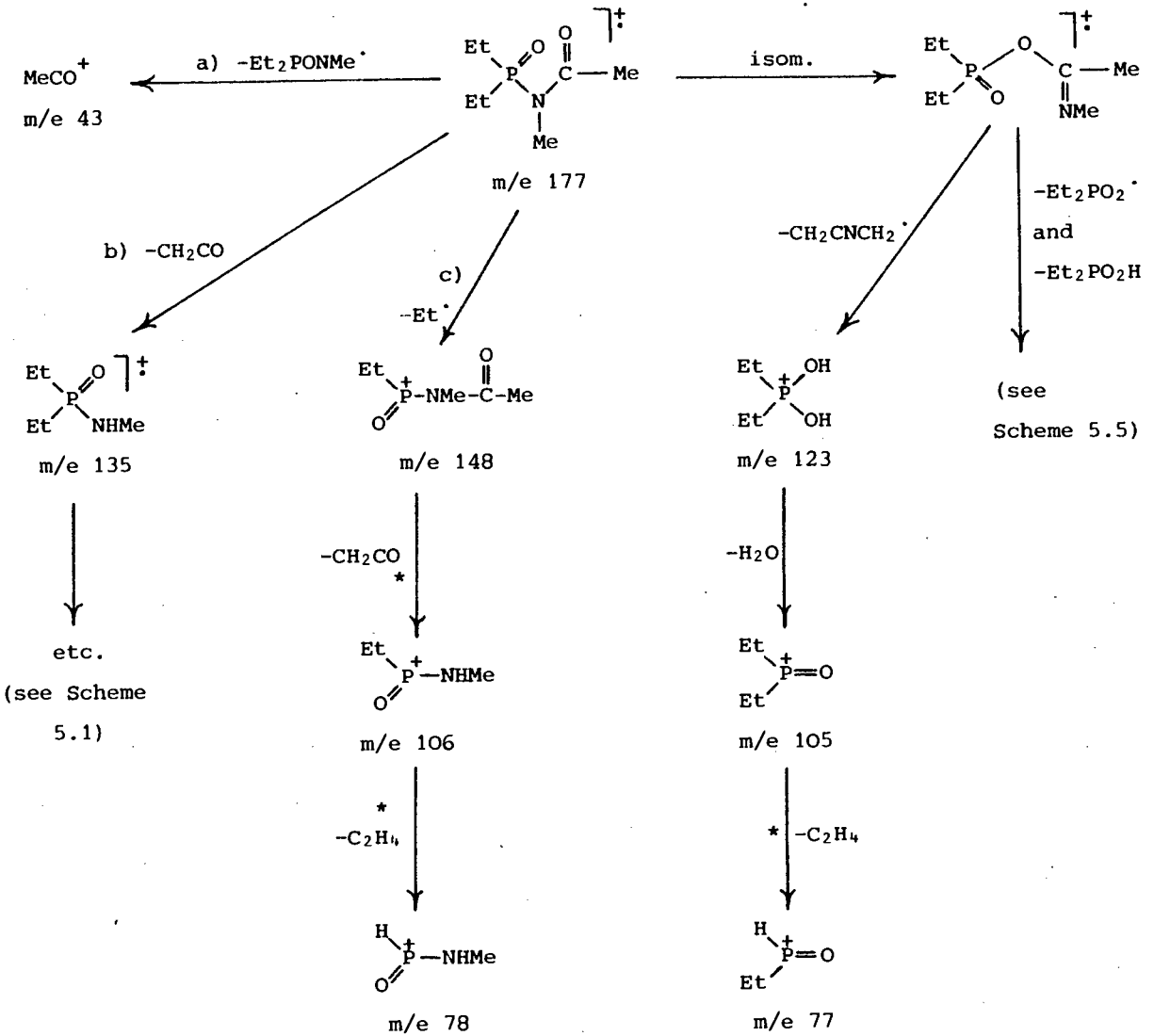
Scheme 5.5


MeCO+
m/e 43
a)
-(MeO)2PONMe•
MeO
MeO
P
O
O
C-Me
N
Me
m/e 181
isom.
MeO
MeO
P
O
O
C-Me
N
Me
b)
-CH2CO
-(MeO)2PO2•
MeC≡N+-Me
m/e 56
-CH2CNMe
-CH2CNCH2
MeO
MeO
P
O
NHMe
m/e 139
(see Scheme 5.1)
-(MeO)2PO2H
CH2=C=N-Me
m/e 55
MeO
MeO
P
O
OH
m/e 126
MeO
MeO
P
OH
OH
m/e 127
-CH2O
H
MeO
MeO
P
O
OH
m/e 96
-H2O
MeO
MeO
P=O
m/e 109
-CH2O
H
MeO
P=O
m/e 79

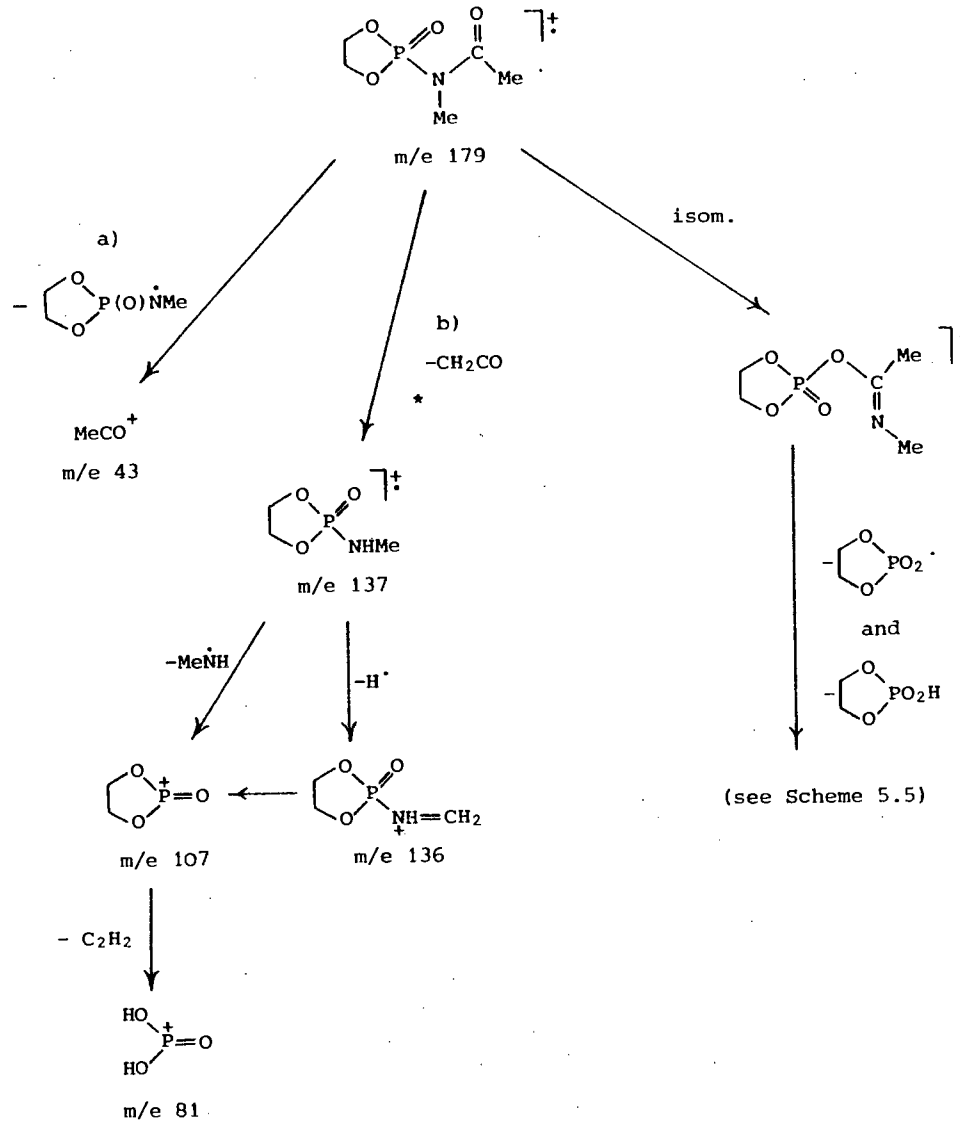
Scheme 5.6


MeCO+
m/e 43
a)
-(EtO)2PONMe·
m/e 209
isom.
b)
-CH2CO
m/e 167
m/e 127
-(EtO)2PO2·
and
-(EtO)2PO2H
(see Scheme 5.5)
-C2H4
*
-EtO·
*
-H2O
-C2H4
*
m/e 139
m/e 122
m/e 109
m/e 99
etc.
(see Scheme 5.1)
-C2H4
*
-H2O
m/e 81

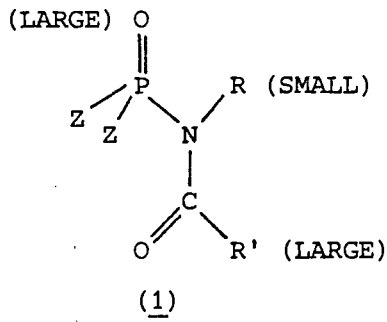
Scheme 5.7


MeCO+
m/e 43
a) -Et2PONMe·
m/e 177
isom.
b) -CH2CO
c)
-Et·
-CH2CNCH2·
-Et2PO2·
and
-Et2PO2H
(see
Scheme 5.5)
m/e 135
m/e 148
m/e 123
etc.
(see Scheme
5.1)
-CH2CO
*
-H2O
m/e 106
m/e 105
*
-C2H4
*
-C2H4
m/e 78
m/e 77

Scheme 5.8


m/e 179
a)
b)
-CH2CO
isom.
MeCO+
m/e 43
m/e 137
-MeNH
-H
m/e 107
m/e 136
- C2H2
m/e 81
and
(see Scheme 5.5)

syn to the carbonyl group, whilst in the phosphylamide system, the tetrahedral geometry of the phosphyl centre facilitates the preferential adoption of the *anti* orientation (see Chapter 4, discussion of secondary amide structural preferences). Representation of the mixed imide system in its most favourable *cis-trans* conformation illustrates the fact that phosphyl N → O (carbonyl) migration is preferred over carboxyacyl N → O (phosphyl) migration:

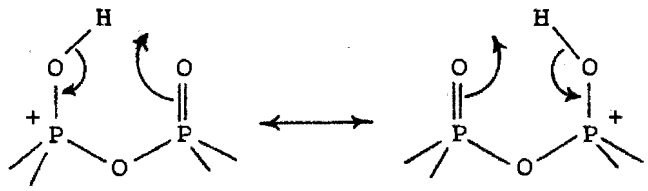


(1)

The mass spectra of three of the tertiary dialkylphosphoryl mixed imides (1c,d,e), are complicated by an additional common feature, namely, the presence of ions of higher m/e values than their corresponding molecular ions, accompanied by fragments obviously derived from these ions. For the sake of clarity, these peaks are not listed in Tables 5.2 and 5.3. The heaviest species in the MS of (1c) has an m/e value of 234, as opposed to the highest value of 290 apparent in the MS of both (1d,e). These species were identified as corresponding to the molecular ions of tetramethyl-(5.10a) and tetraethylpyrophosphate (5.10b) respectively. Analysis of the MS of synthetically prepared (5.10b) enabled an unambiguous identification of the additional artifact ions as having arisen from subsequent fragmentation of (5.10b). Although the MS of (5.10b) has been mentioned in the literature,[120] no fragmentation patterns of this nor other tetraalkyl pyrophosphates were reported. The mass spectrum of (5.10b) was recorded in order to serve the identification purpose of the artifact ions and its fragmentation pattern subsequently analysed in an effort to obtain additional information concerning

the fragmentation behaviour of systems comprising two acyl groups linked via a heteroatom bridge (O or N). The main ions observed are listed in Table 5.4 and the proposed fragmentations illustrated in Scheme 5.9.

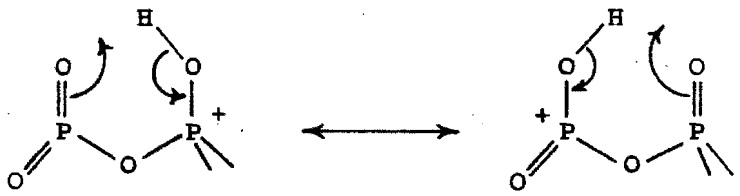
The most obvious fragmentation feature of (5.10b), is the formation of quasiphosphonium ions (5.11) stabilised by both oxygen-phosphorus $p_{\Pi} - d_{\Pi}$ back donation and the charge delocalisation assistance offered by the adjacent phosphoryl group (eq. 5.21):



[5.21]

(5.11)

The major fragmentation pathway of the molecular ion, involves loss of vinyl radical from one of the peripheral ester functions via a double hydrogen transfer (Scheme 5.9, pathway b), to produce a stabilised quasiphosphonium ion (m/e 263). The subsequent fragmentation sequence: m/e 263 → 235 → 207 → 179 involves successive elision of three molecules of ethylene via the McLafferty rearrangement. The stability of these ions is reflected in their high intensities (99, 62, 48 and 79% of the base peak respectively). Another pathway available to the ions (5.11) is dehydration to yield the analogously stabilised protonated phosphoric-metaphosphoric anhydride system (5.12) (eq. 5.22):[121]



[5.22]

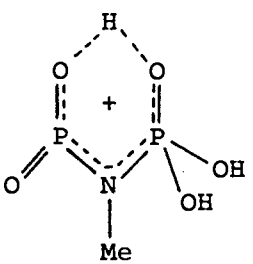
(5.12)

It has been found that fragmentation to yield ions stabilised by charge delocalisation into an adjacent acyl group, is not limited to the pyrophosphate (5.10b), but is also observed in the mass spectra of the diacyl compounds (5.9b) and (5.13). One of the major fragmentations exhibited

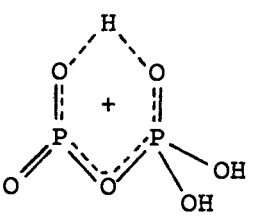
$(EtO)_2P(O)-NMe-P(O)(OEt)_2$ (5.9b)

$(EtO)_2P(O)-CH_2-C(O)Me$ (5.13)

by the phosphoric imide (5.9b), is loss of vinyl radical (Scheme 5.10, pathway c) to produce a stabilised quasiphosphonium ion m/e 276, which is capable of eliminating ethylene (m/e 276 → 248 → 220 → 192) as indicated in Scheme 5.10. The analogy between the related systems (5.9b) and (5.10b), is illustrated by the structural similarity of their corresponding base peaks:

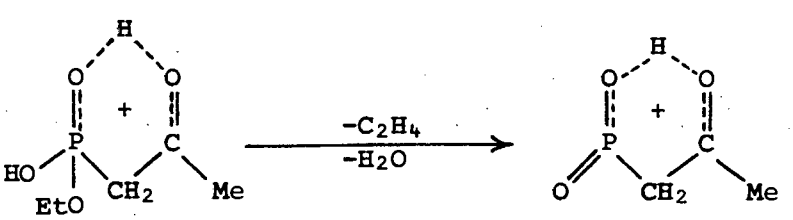


m/e 174



m/e 161

Loss of vinyl radical from the molecular ion of the β-ketophosphonate (5.13), results in the formation of a quasiphosphonium ion stabilised by participation of the neighbouring acetyl group in charge delocalisation (Scheme 5.11, pathway b). Loss of ethylene (m/e 167 → 139) followed by dehydration, leads to the formation of a resonance-stabilised β-ketophosphonylium ion (eq. 5.23):



[5.23]

Table 5.4 Main ions in the mass spectrum of tetraethylpyrophosphate (5.10b).

m/e	47	65	81	99	109	127	143	145
I%	6	15	59	55	4	14	6	14
m/e	161	163	179	189	191	207	217	
I%	100	10	80	20	23	44	14	
m/e	218	235	245	246	263	290		
I%	15	61	9	14	100	16		

Table 5.5 Selected ions in the mass spectrum of N-methyl tetraethylimidophosphate (5.9b) (M^+ 303).

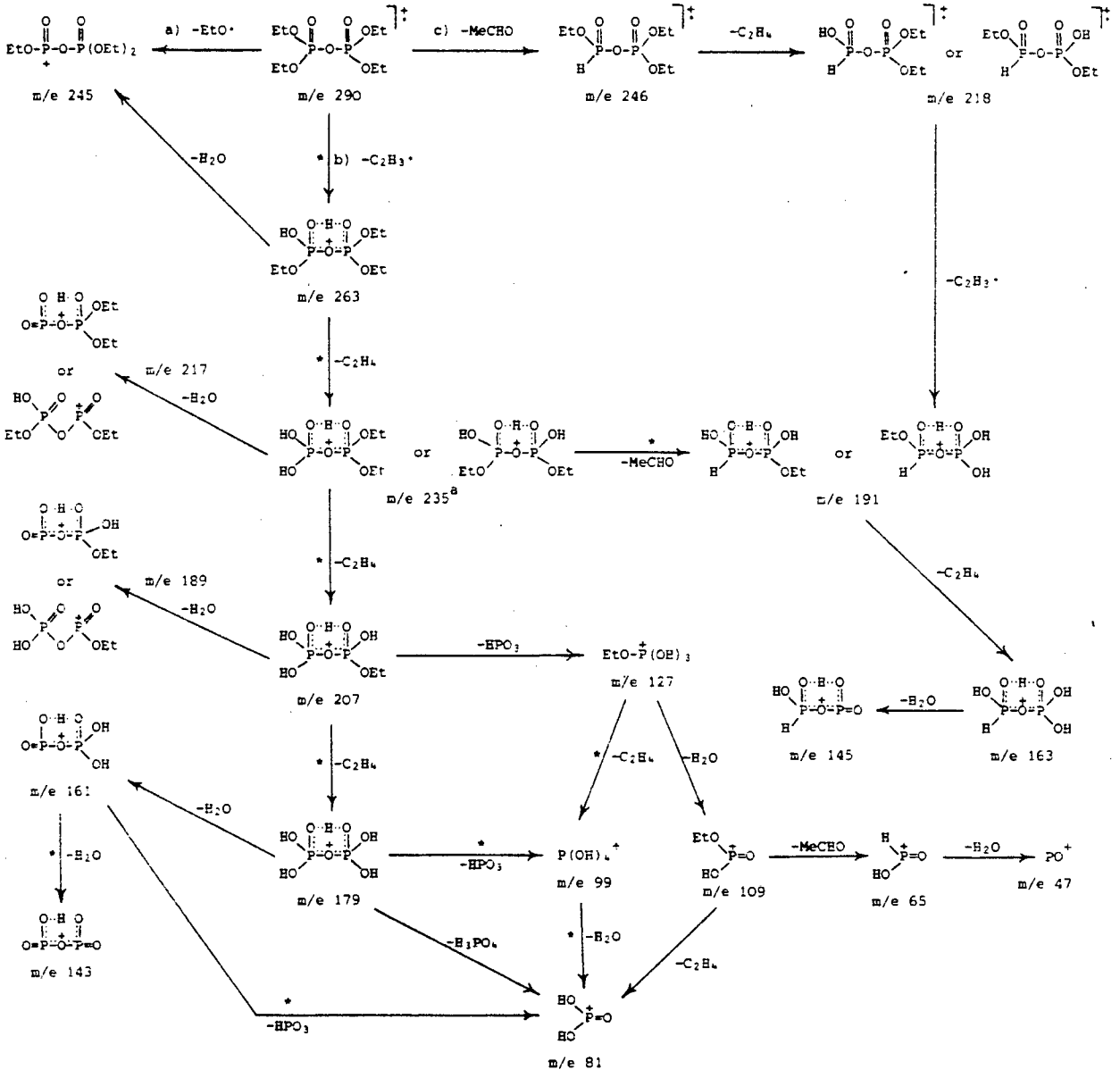
m/e	156	167[a]	174	192	202	
I%	10	51	100	18	17	
m/e	203	219	220	230	231	
I%	12	10	24	12	21	
m/e	247	248	259	275	276	303
I%	26	28	20	38	24	68

[a] For the purpose of clarity, ions produced by subsequent fragmentation of amidate (5.1b) (M^+ 167) have been omitted (Scheme 5.1, Table 5.1).

Table 5.6 Main ions in the mass spectrum of diethyl acetyl phosphonate (5.13) (M^+ 194).

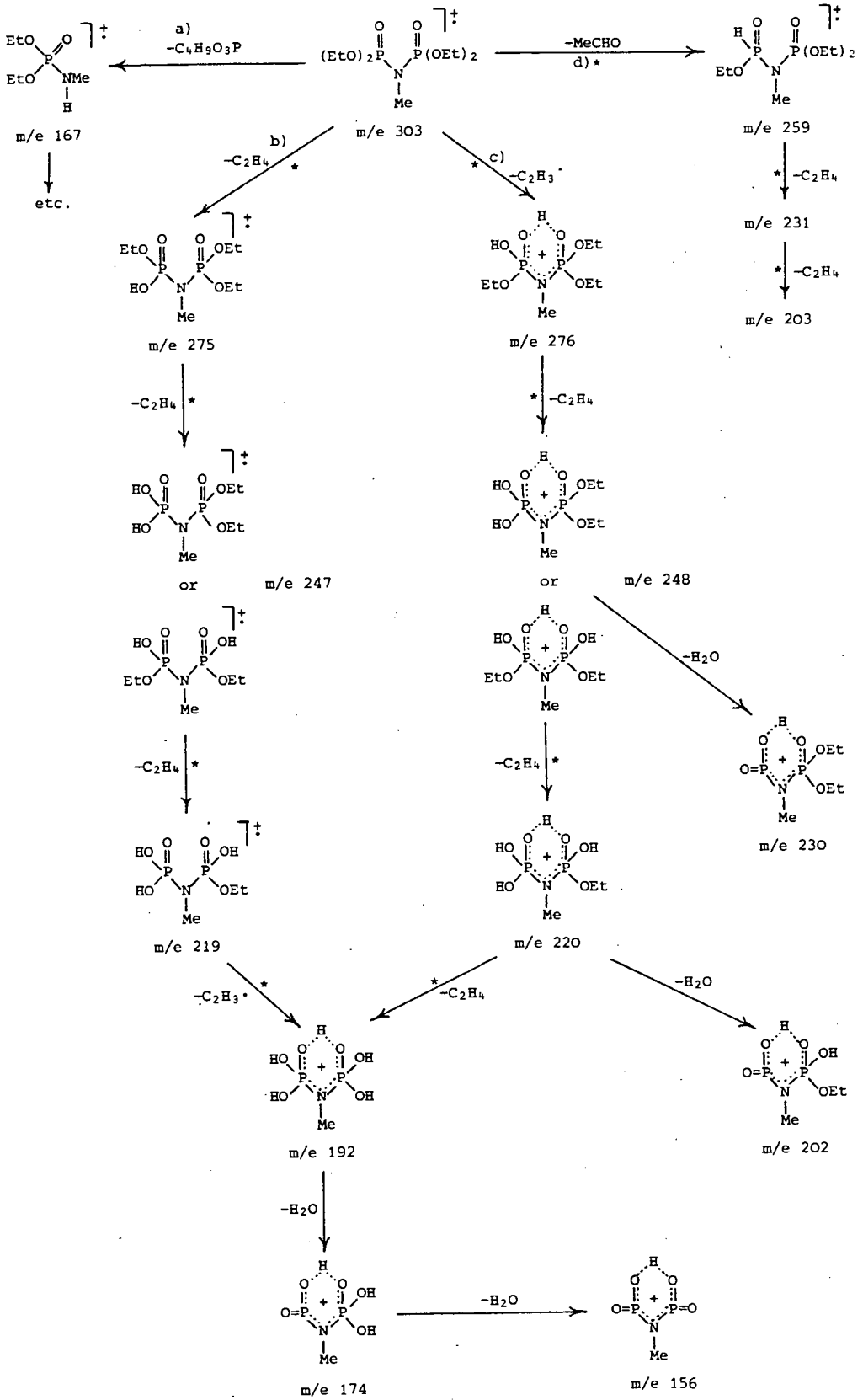
m/e	43	79	81	97	109	121	123	125	139
I%	100	11	36	66	40	44	39	77	17
m/e	149	151	152	167	179	194			
I%	23	19	56	19	22	33			

Scheme 5.9

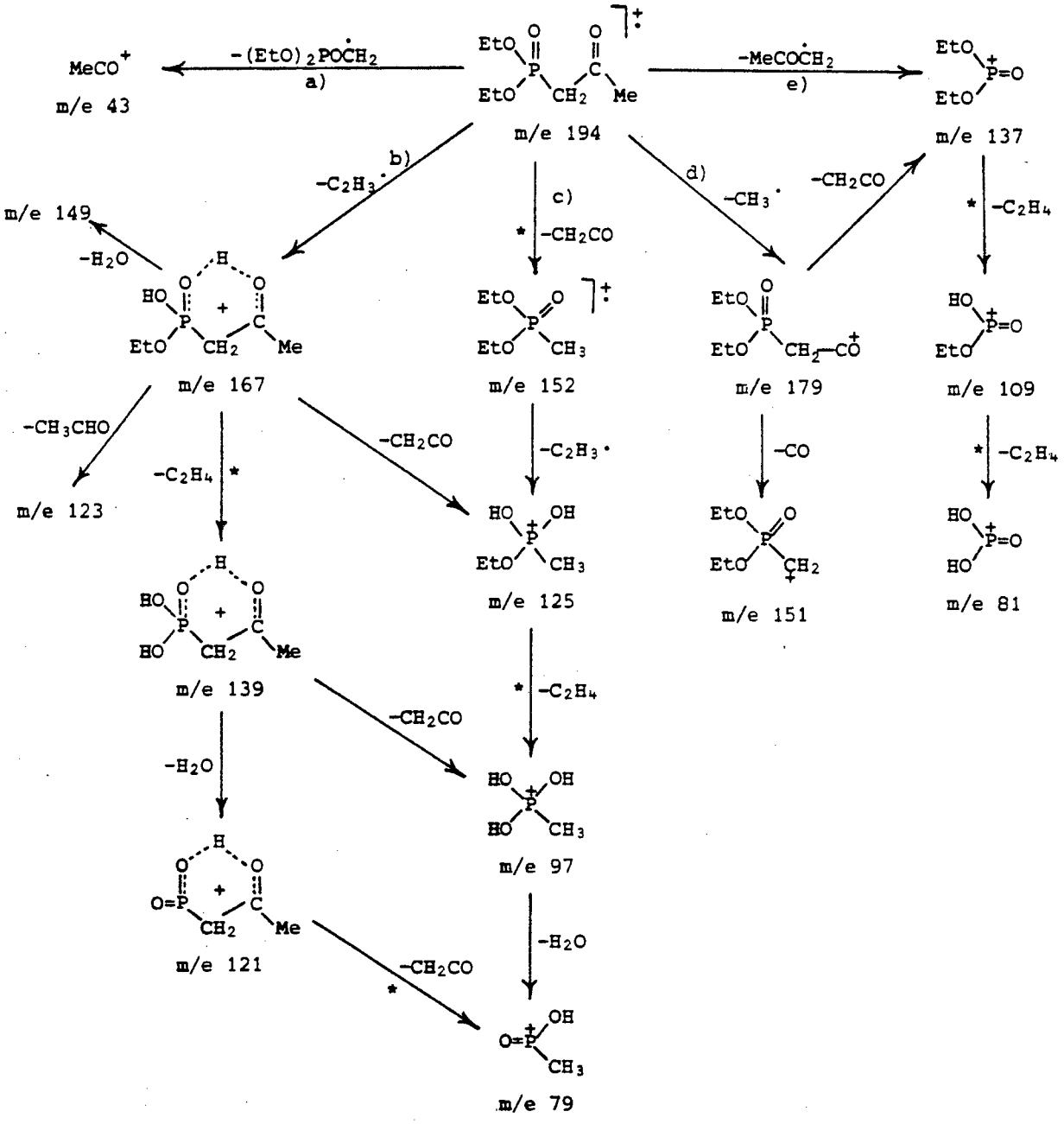


[a] The ion m/e 235 probably has a predominantly symmetrical structure (P_1, P_2 diethyl ester): the unsymmetrical ion would be more susceptible to loss of water rather than ethylene, giving rise to a more intense m/e 217 than m/e 207 and m/e 189 than m/e 179 ion, respectively. In fact the reverse is observed, with ions resulting from C_2H_4 elimination predominating over dehydration products.

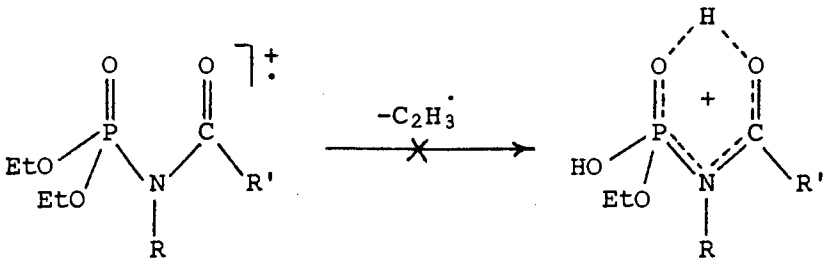
Scheme 5.10


a)
$-C_4H_9O_3P$
m/e 167
etc.
m/e 303
-MeCHO
d)*
m/e 259
m/e 231
m/e 203
b)
$-C_2H_4$
c)
$-C_2H_3$
m/e 275
m/e 276
or
m/e 247
or
m/e 248
$-H_2O$
m/e 230
m/e 219
m/e 220
m/e 192
m/e 202
m/e 174
m/e 156

Scheme 5.11


MeCO+
m/e 43
-(EtO)2POCH2
a)
m/e 194
-MeCOCH2
e)
m/e 137
b)
-C2H3·
c)
*-CH2CO
d)
-CH3·
-CH2CO
*-C2H4
m/e 149
-H2O
m/e 167
m/e 152
m/e 179
m/e 109
-CH3CHO
m/e 123
-C2H4 *
-CH2CO
-C2H3·
-CO
*-C2H4
m/e 125
m/e 151
m/e 81
m/e 139
*-C2H4
-CH2CO
-H2O
m/e 97
m/e 121
-CH2CO
*
-H2O
m/e 79

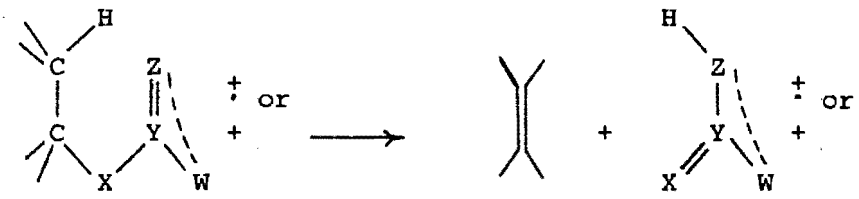
The diethylphosphoryl mixed imides (1b,d,e) thus differ from the related diacyl compounds (5.9b, 5.10b, 5.13), in that loss of $C_2H_3^{\cdot}$ and formation of a carboxyacyl-stabilised quasiphosphonium ion is not a competitive fragmentation pathway:



(1b,d,e)

According to eq. 5.14a, an ethyl phosphate ester radical ion with the positive charge located at the phosphoryl oxygen, can undergo expulsion of vinyl radical to form a quasiphosphonium ion, via a double hydrogen transfer. The diethylphosphoryl compounds (5.9b, 5.10b, 5.13) are all capable of yielding molecular ions resulting from phosphoryl oxygen electron removal, from which $C_2H_3^{\cdot}$ expulsion can occur. The absence of $C_2H_3^{\cdot}$ loss from (1b,d,e), is therefore consistent with the preferential localisation of the radical ion character in the N—C(O) rather than N—P(O) moiety of the mixed imide system. This provides an example illustrating the fragmentation pattern dependence upon the molecular ion structure.

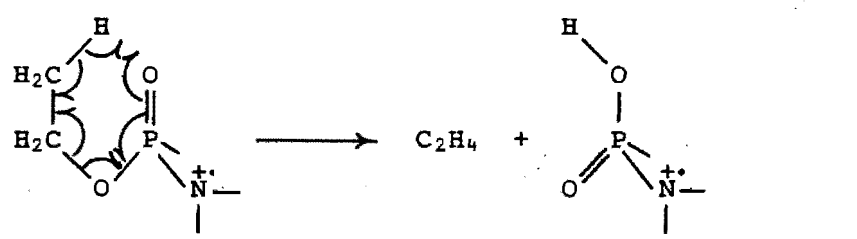
In view of the facile expulsion of ethylene from the quasiphosphonium ions produced by initial loss of $C_2H_3^{\cdot}$ from the pyrophosphate (5.10b), the absence of ethylene loss from the molecular ion itself is particularly conspicuous. The McLafferty rearrangement operates for ions or radical ions capable of electronic shift within the six-centre transition state of the following molecular skeleton:[107]



[5.24]

(5.14)

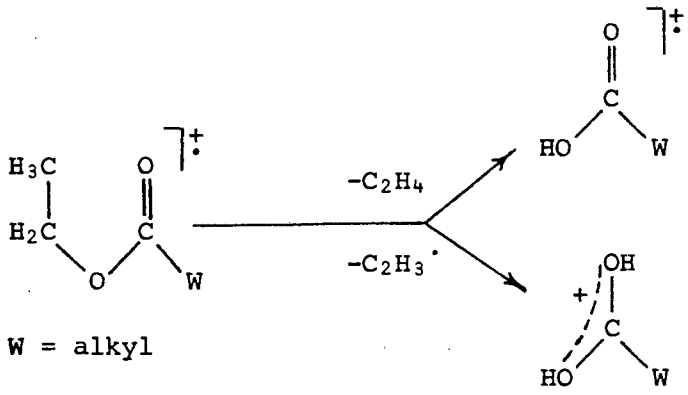
The ability of a radical ion to undergo a McLafferty rearrangement appears to be a sensitive function of the specific site of the positive charge and is thus dependent upon the nature of W, X, Y and Z in the precursor. In this work, the loss of ethylene has been observed from the following radical ions: $(EtO)_2P(O)NHMe^{\rceil\cdot+}$, $(EtO)(HO)P(O)NHMe^{\rceil\cdot+}$, $(EtO)(H)P(O)NHMe^{\rceil\cdot+}$, $(EtO)_2P(O)NMeP(O)(OR)_2^{\rceil\cdot+}$ (R = Me, Et) and $(EtO)_2P(O)NHC(O)Ph^{\rceil\cdot+}$; in all cases but the last, the fragmentation is metastable-supported. Similarly, metastable-supported ethylene loss from the phosphoramidate radical ions $(EtO)_2P(O)NH_2^{\rceil\cdot+}$ [101] and $(EtO)_2P(O)NHPh^{\rceil\cdot+}$ [105a] have been reported. On the other hand, it was found that McLafferty-type elimination does not occur from precursors such as $(EtO)_2P(O)—O—P(O)(OEt)_2^{\rceil\cdot+}$, $(EtO)_2P(O)CH_2C(O)Me^{\rceil\cdot+}$, $(EtO)_2P(O)Cl^{\rceil\cdot+}$, $(EtO)_2P(O)H^{\rceil\cdot+}$ and $(EtO)_2P(O)R^{\rceil\cdot+}$ (R = alkyl).[123] The behaviour of $(EtO)_3P(O)^{\rceil\cdot+}$ is more ambiguous, since although McLafferty[124] reports the existence of a low intensity (2.8%) [M - 28] peak in its MS, this peak is absent in the spectrum recorded by Bafus *et al.*,[105b] where all ions of intensity I > 2.5% have been listed. The implication of these observations is that the elimination of ethylene is facilitated in phosphoramidate systems (W = N) by localisation of the positive charge at the nitrogen atom (eq. 5.25):



[5.25]

In contrast, precursors in which W = H, Cl, aryl, O-alkyl and O-phosphoryl preferentially localise the positive charge at the phosphoryl oxygen, thus facilitating $C_2H_3^{\bullet}$ loss (double H transfer) over C_2H_4 loss (single H transfer).

However, the structural factors affecting these two competing pathways in phosphoryl radical ions (5.14; Y = P, Z = O) do not extend to their carboxyacyl analogues (5.14; Y = C, Z = O); whereas ethylphosphoramidates (eg. 5.1b, 5.9a,b) undergo loss of both C_2H_4 and $C_2H_3^{\bullet}$ (indicating the existence of two types of molecular ion with the $^{+\bullet}$ character at either nitrogen or oxygen), ethyl carbamates exclusively expel C_2H_4.[113] In addition, the loss of both C_2H_4 and $C_2H_3^{\bullet}$ from ethyl carboxylic esters has been observed (eq. 5.26):[125]



W = alkyl

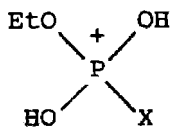
[5.26]

This dual fragmentation of ethyl carboxylates contrasts the exclusive $C_2H_3^{\bullet}$ loss exhibited by ethyl phosphates, suggesting the participation of additional factors, besides the charge localisation in the precursor radical ion, in determining the fragmentation preference. One such determining factor may be the relative stabilities of the products formed via loss of $C_2H_3^{\bullet}$ and C_2H_4 respectively. As has been discussed above, vinyl radical expulsion from a phosphate ester radical ion results in the formation of a highly stabilised quasiphosphonium ion and is thus a favoured fragmentation pathway, particularly when the positive charge is located at the phosphoryl oxygen. Quasiphosphonium ion formation may thus be viewed as part of the

driving force for $C_2H_3^{\cdot}$ (as opposed to C_2H_4) loss. In contrast, the relatively low stability of the analogous protonated carboxylic acid species formed via $C_2H_3^{\cdot}$ loss from an ethyl carboxylate discourages this pathway, thus enabling fragmentation via the competitive C_2H_4 loss pathway to occur (eq. 5.26).

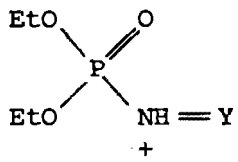
It is of interest to note that in solution, protonated carboxylic acids are much less stable than their protonated phosphoric analogues. For example, the pK_a value of protonated acetic acid, $MeC(OH)_2^+$, as determined in strong aqueous acid, is more than two log. units less than the pK_a of the conjugate acid of dimethylphosphinic acid, $Me_2P(OH)_2^+$.[126]

The McLafferty rearrangement has also been confirmed in this work and elsewhere to operate for a variety of phosphoryl-containing ions (as opposed to radical ions) in which the ethoxyl function is in the vicinity of the positive charge. The ions susceptible to ethylene loss can be categorised into three structurally different classes: (i) quasiphosphonium ions (5.15); (ii) phosphoryl derivatives containing a positively-charged atom directly bound to phosphorus (5.16), and (iii) phosphorylium ions (5.17). Examples of (5.15 - 5.17) observed in this work are given below.



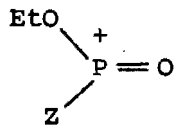
(5.15)

X = H, OH, $OP(O)(OR)_2$, $NMeP(O)(OR)_2$



(5.16)

Y = CH_2, CO



(5.17)

Z = OH, NHMe, OEt

In all cases, strong electron deficiency developed at or near the phosphorus atom facilitates the elimination reaction.

The formation of tetraalkyl pyrophosphate from the mixed imides (1c-e) represents a problem in itself. The fact that formation of a symmetrical anhydride from a mixed imide precursor necessarily proceeds via a bimolecular mechanism, suggests the possibility of thermal disproportionation at the inlet, prior to entry into the ionisation chamber. By recording the mass spectrum of (1d) at constant ionising energy (70 eV) but at variable ion source temperature, it was found that the intensity of the artifact ions diminishes with decreasing temperature, supporting the proposed thermal origin of the disproportionation. At 200°C (the standard temperature for all spectra in this work), the molecular ion of tetraethylpyrophosphate appears as an ion (m/e 290) of intensity 4.2%; at 100°C, an intensity decrease to 1.4% is observed and at 60°C, the m/e 290 ion, as well as all ions resulting from its subsequent fragmentation, are absent. Thermal artifact formation is apparently common in the mass spectra of organophosphorus compounds; Ramirez *et al.*[127] have reported the appearance of numerous artifacts in the mass spectra of phosphate esters, which presumably arise via condensation/dehydration processes.[128] The most obvious reaction leading to the pyrophosphate system (5.10), is thermal dehydration of the dialkylphosphate (5.18) (eq. 5.27):

$$\underset{(5.18)}{2(RO)_2PO_2H} \xrightarrow[-H_2O]{\Delta} [(RO)_2P(O)]_2O \qquad [5.27]$$

Haake *et al.*[129] have found that dialkylphosphinic acids R_2PO_2H undergo thermal dehydration to their corresponding anhydrides under typical MS recording conditions, supporting the proposed pyrophosphate origin given in eq. 5.27.

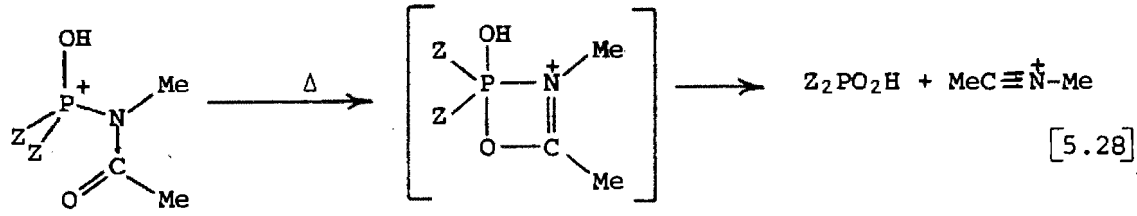
5.2.3 LOW ENERGY MASS SPECTROMETRY

The mixed imide radical ions generated by bombardment with a 70 eV energy electron beam, are capable of undergoing numerous and diverse fragmentations.

In an attempt to categorise the fragmentations according to their energy requirements, an analysis of the mass spectra of selected substrates recorded at substantially lower beam energies was carried out. The mass spectral changes of (1f) that occur within the 6.5 - 13 eV nominal beam energy range are illustrated in Fig. 5.1. The appearance of the ions of m/e 55 and 148 in the 10 eV spectrum indicates that isomerisation (and subsequent fragmentation of the imidate radical ion) and loss of ethyl radical are the two lowest energy pathways available to the molecular ion. An increase in the nominal beam energy to 13 eV results in the appearance of ions derived from the loss of ketene from the molecular ion (Scheme 5.7, pathway b), suggesting a relatively high energy requirement for this McLafferty-type process. It is of interest to note that the fragmentation pathway of highest energy involves homolytic N-acetyl fission of the molecular ion to yield the acetylium ion (m/e 43, pathway a); a significant contribution of this pathway requires a beam energy of almost 15 eV.

The low energy mass spectra of the secondary N-benzoyl substrate (1b) analogously indicate an extremely low energy isomerisation process, as opposed to a high energy N-benzoyl fission process. In an attempt to quantify the energy requirement for the latter fragmentation, the absolute areas of the molecular ion and benzoylium ion peaks were monitored over the appropriate narrow beam energy ranges, yielding the linear plots shown in Fig. 5.2. The Linear Extrapolation Method[130] was applied in estimating the ionisation potential of the substrate (IP, 9.0 eV) and the appearance potential of benzoylium ion (AP, 12.2 eV) from the intercepts of the respective appearance plots. The energy requirement for N-benzoyl fission is approximated by the difference between the above quantities, i.e. 3.2 eV. The application of this technique to the determination of the energy requirements for other mixed imide fragmentation processes is currently under further investigation.

The spectra of (1a,b,c,d,f) recorded at sub-ionisation potential beam energies (see for example the 6.5 eV spectrum of (1f) in Fig. 5.1a), exhibit an interesting common feature, namely, the presence of a relatively abundant (M + 1) peak,[131] probably corresponding to the quasiphosphonium ion structure $Z_2\overset{+}{P}(OH)$-NR-COR' (5.19). However, in the case of the tertiary N-acetyl substrates (1c,d,f), a very prominent accompanying peak at m/e 56, corresponding to N-methyl acetonitrilium ion, is observed. A possible origin of the nitrilium ion from thermal rearrangement of the corresponding quasiphosphonium ion (5.19), followed by expulsion of the acid Z_2PO_2H, is illustrated in eq. 5.28:



[5.28]

(5.19)

In contrast, there is no evidence for the formation of the analogous N-protonated benzonitrilium ion (m/e 104) in the 6.5 eV spectra of the secondary N-benzoyl substrates (1a,b). The thermal reaction of the type given in eq. 5.28 is of particular interest, since it offers a source of acid, Z_2PO_2H that is capable of undergoing subsequent thermal dehydration and in this regard, the persistence (or lack thereof) of this rearrangement reaction at higher beam energies (e.g. 70 eV), may be related to the selective thermal disproportionation of the mixed imides (1c,d,e) to their corresponding tetraalkylpyrophosphates (eq. 5.27). However, by virtue of the preliminary nature of these results, this proposal remains speculative.

Figure 5.1 Fragmentation pattern dependence of (1f) upon the nominal beam energy (ion source temperature 200 - 220°C).

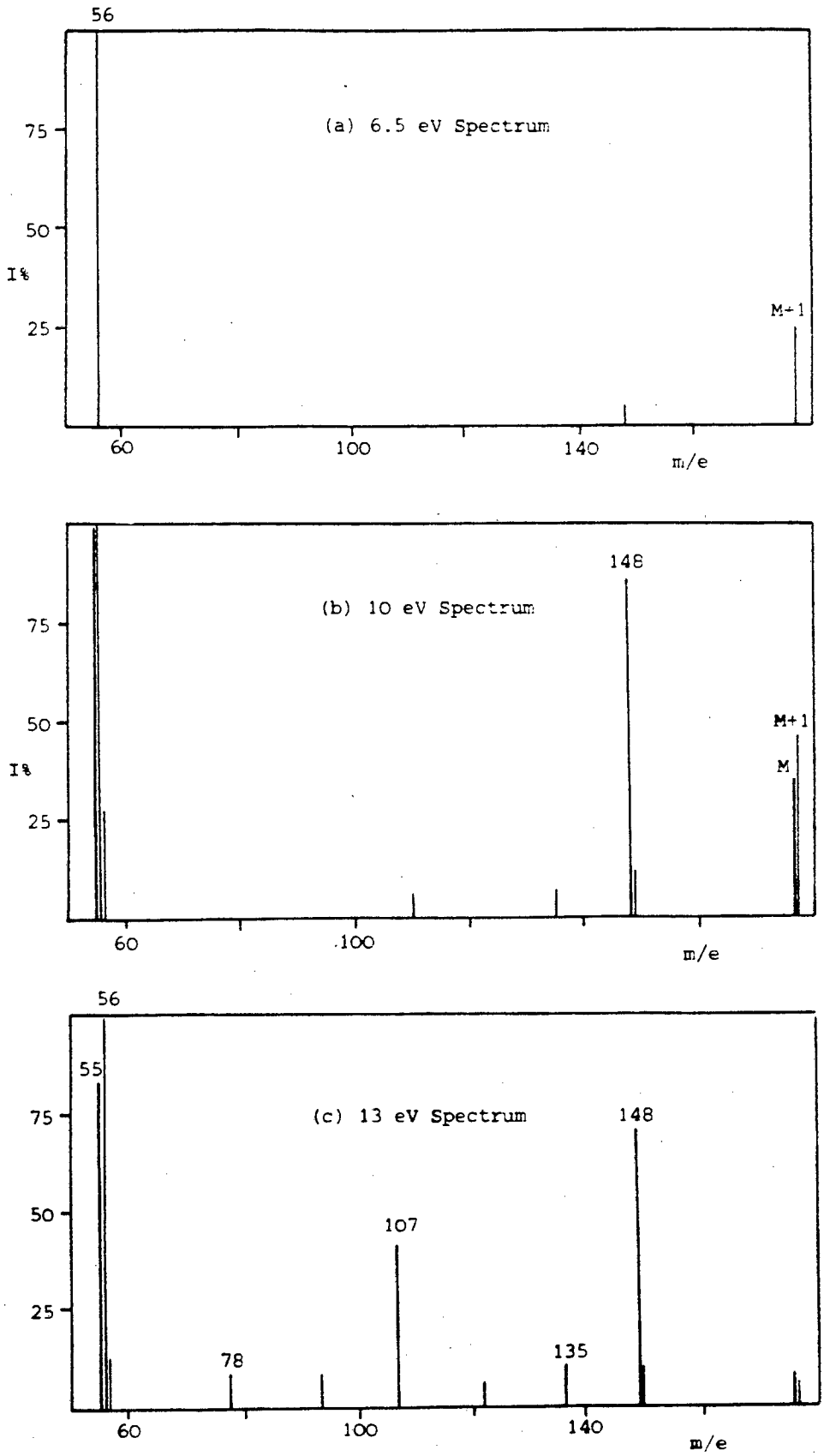
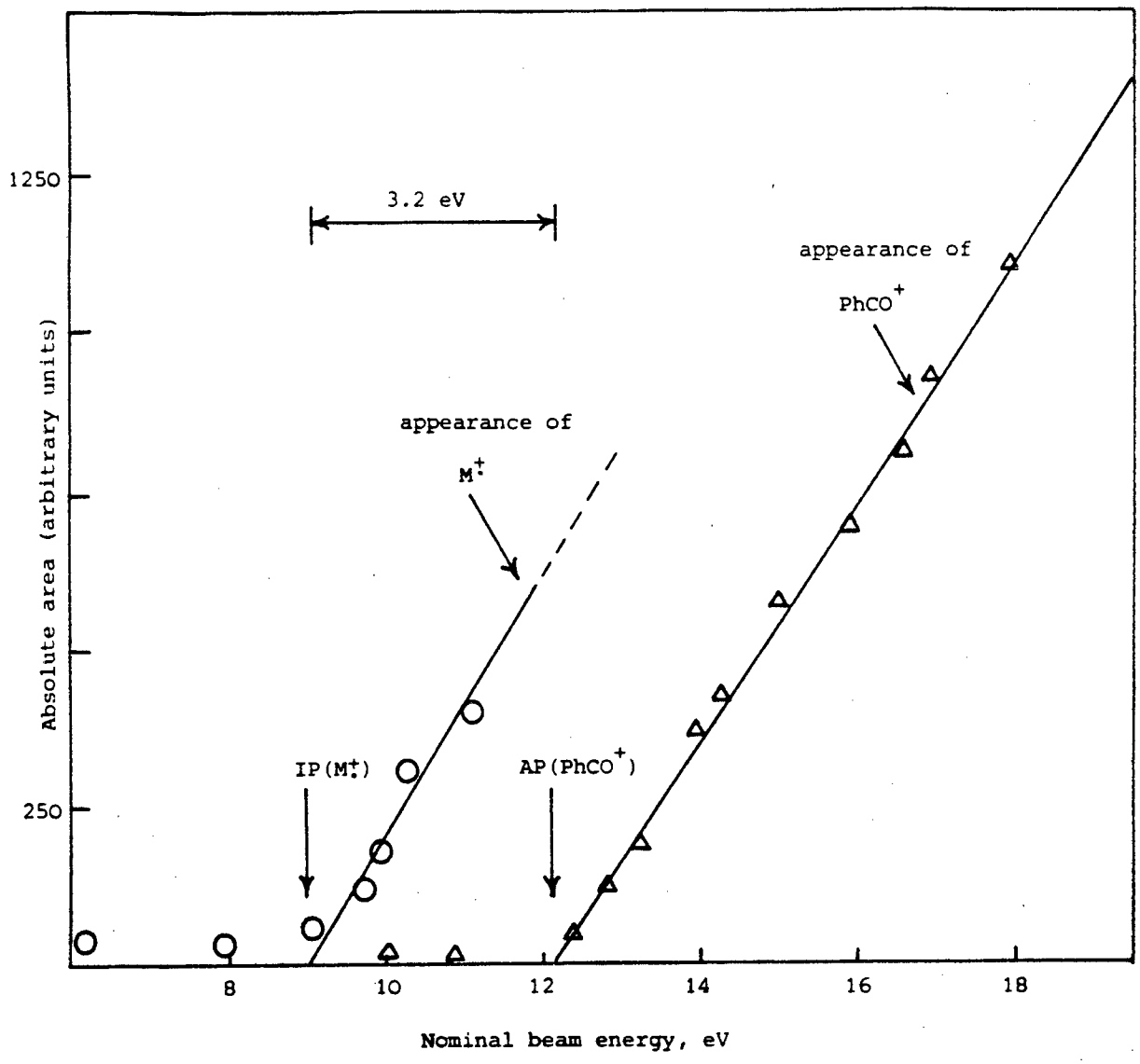


Figure 5.2 The ionisation efficiency curves of:

(i) the molecular ion of (1b) (— O —);

(ii) the benzoylium ion fragment (— Δ —).



CHAPTER 6

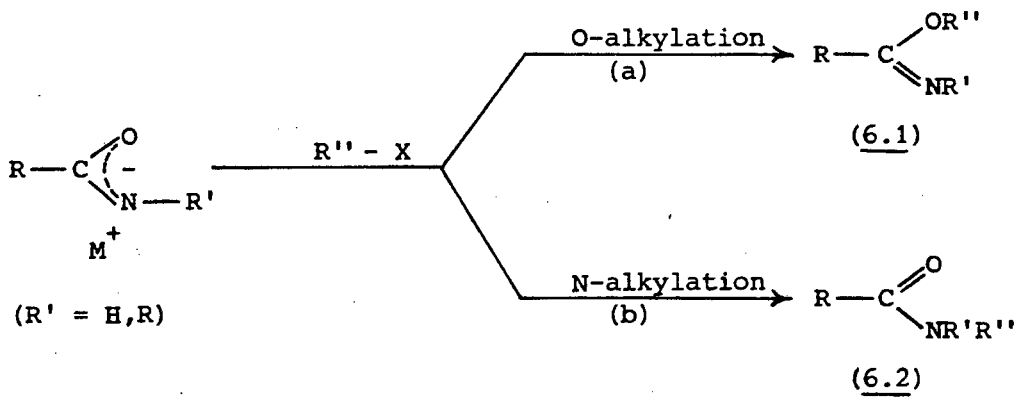
Nucleophilic Behaviour of N-Benzoyl Dimethyl -phosphoramidate

6.1 INTRODUCTION

In the past, insight into the nucleophilic properties of the carboxamide moiety has been gained by investigating the reactions of carboxylic amides with alkylating agents.[132] The substrate reactivity and the site of alkylation are related to the form in which the amide exists, whether neutral, as its conjugate acid or as its conjugate base and hence, to the experimental conditions. Alkylation under neutral conditions with the amide present in its unionised form is generally sluggish, as expected from its weak basicity and requires the use of powerful alkylating agents such as alkyl sulfates, oxonium salts and diazoalkanes. Although alkylation under acidic conditions is usually difficult, protonation of the alkylating agent[133] is one way in which the acid may catalyse the alkylation reaction. Selectivity is greatly enhanced under acidic conditions and even at low temperatures, only products arising from N-alkylation are observed.

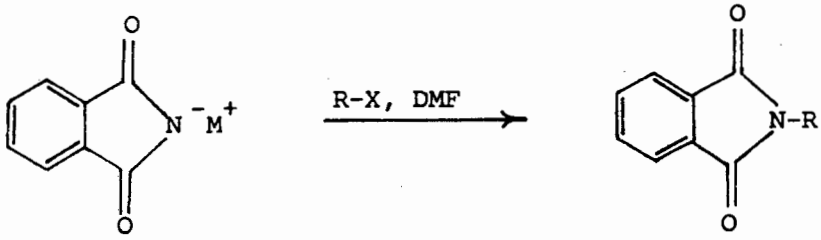
The most synthetically useful and facile alkylation reactions are those occurring under basic conditions. Primary and secondary amides, in the presence of a base, preferentially alkylate at nitrogen,[134] thus introducing a selectivity factor absent in the analogous alkylations under neutral conditions. The general scheme for the alkylation of the conjugate base of a primary or secondary carboxylic amide is given below.

Scheme 6.1



Experimental evidence, in particular the observed thermal interconversion of (6.1) → (6.2) via the Chapman Rearrangement,[132,135] suggests that the O-alkyl imidate (6.1) is the product of kinetic control, whereas the N-alkyl amide (6.2) is the product of thermodynamic control.[136] As a result, the overall contributions of the pathways leading to the O- and N-alkylated products respectively, depend not only upon the form in which the amide exists, but also upon additional factors such as the strength of the alkylating agent, the reaction temperature and the nature of the solvent.

The most widely studied alkylation reaction of carboxylic imides is the first step of the Gabriel synthesis of amines[137] involving the exclusive N-alkylation of the metal salt of a cyclic imide, such as phthalimide, with an alkyl halide as alkylating agent:

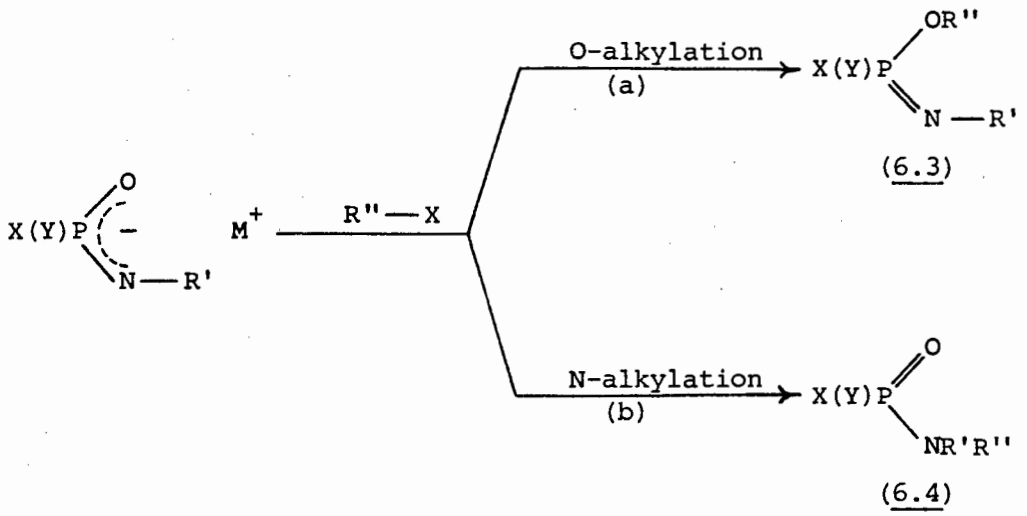


[6.1]

In contrast, the available information on the reactivity of acyclic carboxylic imides towards alkylating agents is extremely scarce.[138]

Recent studies have shown that phosphylamidates behave in a similar manner to their carboxylic analogues with respect to their nucleophilic reactions, giving rise to a kinetic (O-substituted phosphylamide) product and a thermodynamic (N-substituted phosphylamide) product (Scheme 6.2).[5,139] The product proportions are similarly influenced by the factors discussed above.

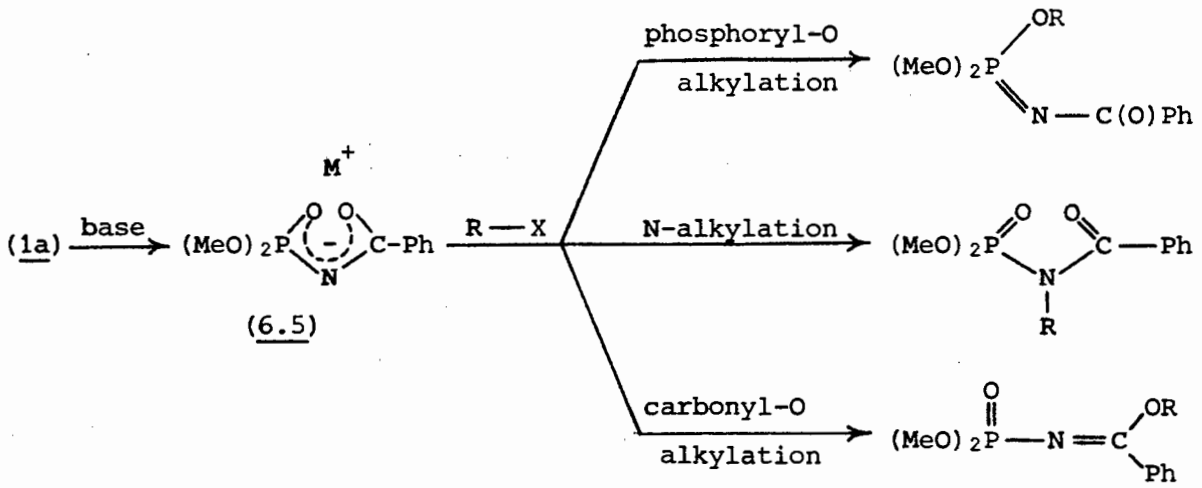
Scheme 6.2



Selective N-substitution can be achieved under basic conditions and at elevated temperatures, to yield the N-substituted phosphylamidate (6.4).[140-142] In view of the hydrolytic instability of the product (6.4) under mildly acidic conditions, this selective N-alkylation reaction has found diverse applications, notably in the synthesis of amines[28,143] and peptides.[144]

Initial investigation has revealed that the secondary mixed imide, N-benzoyl dimethylphosphoramidate, (1a), is too weakly nucleophilic to react with even the strongest of alkylating agents under neutral conditions. However, nucleophilic enhancement is achieved by generating the anion (6.5) in the presence of base, and subsequent alkylation can lead to the formation of three isomeric products:

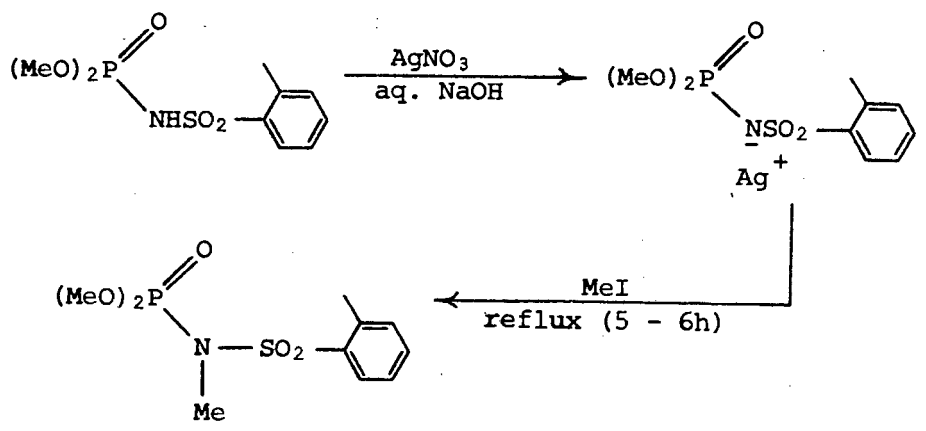
Scheme 6.3



The distribution of negative charge within the OPNCO fragment of (6.5) determines the relative strengths of the three nucleophilic centres. This, in turn, influences the extent to which the nucleophilic behaviour of the parent carboxylic and phosphoric amides is retained in the mixed system. Paying due consideration to the above, a study of the alkylation of (6.5) under a variety of conditions was undertaken.[145] In addition, an evaluation of the feasibility of utilising N-alkylation of the anion generated from a secondary (and easily accessible[15]) N-acyl phosphoric amide, as a synthetic route to the less accessible tertiary derivatives (Chapter 2), was envisaged as an important corollary of such an investigation.

6.2 RESULTS AND DISCUSSION

The initial attempt at alkylating the anion (6.5) was based upon the report in which Shevchenko and Derkach[146] claim facile and exclusive N-methylation of the silver salt of N-(2-methylphenyl)sulfonyl dimethylphosphoramidate with methyl iodide (eq. 6.2):



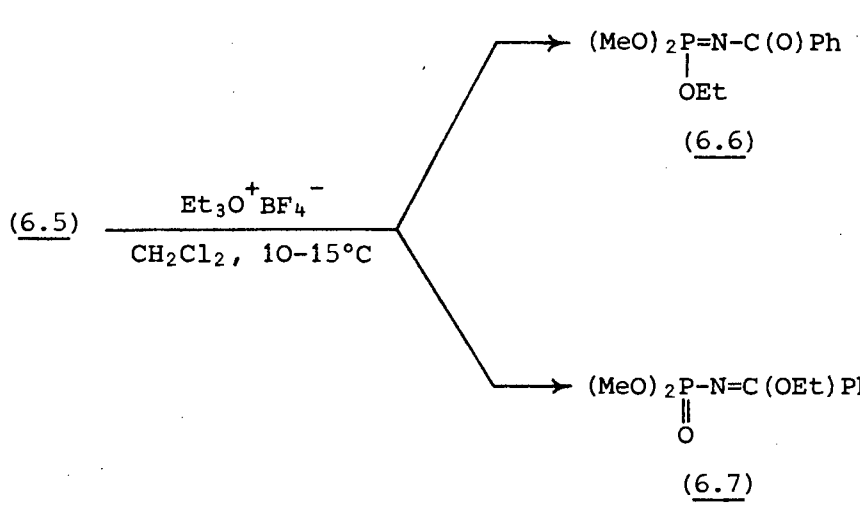
[6.2]

However, the analogous reaction between the silver salt of (1a) (6.5; M = Ag) and methyl iodide failed to yield any methylation products. Other preliminary investigations revealed that the sodium salt of (1a) (6.5; M = Na), which is smoothly formed by reaction of (1a) with sodium hydride, reacts

extremely sluggishly with alkylating agents such as methyl and ethyl iodide, even with prolonged reflux in benzene, DMSO or THF. The weak nucleophilicity of the mixed imide anion could be a consequence of extensive charge delocalisation within the OPNCO fragment, or could be due to the tightness of the ion pair in (6.5), leading to poor charge separation and solvation. In an attempt to enhance the nucleophilicity of the anion by "baring" it, the reaction of the sodium salt (6.5) with ethyl iodide in benzene was carried out in the presence of a catalytic amount of 18-crown-6.[147] However, the addition of the crown ether offered no improvement. This is consistent with the fact that its ring size renders it a more effective chelating agent for potassium than sodium ion.[148] In view of the above, the need to employ more severe reaction conditions to effect alkylation of (6.5) was apparent.

6.2.1 ETHYLATION WITH TRIETHYLOXONIUM TETRAFLUOROBORATE

An efficient and smooth ethylation of the sodium salt (6.5) was accomplished at low temperature using the powerful alkylating agent, triethyloxonium tetrafluoroborate in methylene chloride. The ^{1}H NMR spectrum of the product mixture obtained after stirring for 5 h is shown in Fig. 6.1. This ethylation reaction gives rise to two products, which were separated by column chromatography and identified by ^{1}H NMR and IR spectroscopy as the phosphoryl oxygen-ethylated (6.6) and carbonyl oxygen-ethylated derivatives (6.7):



[6.3]

Both the N-acyl trialkylphosphorimidates[16,149] and the N-phosphoryl-imidates[18,19,149d,150] have been the subjects of numerous synthetic and infrared spectral investigations. Such compounds have, in the past, been prepared by the modified Michaelis-Arbusov syntheses indicated in eqs. 6.4[16] and 6.5:[150a]

$$ArCON_3 + (RO)_3P \longrightarrow ArC(O)N{=}P(OR)_3 + N_2 \qquad [6.4]$$

$$(RO)_3P + Cl{-}N{=}C(OR')(R'') \longrightarrow R''C(OR'){=}N{-}P(O)(OR)_2 + RCl \qquad [6.5]$$

The alkylation reaction given in eq. 6.3 thus constitutes a novel route to both types of compounds from a common N-acyl phosphoramidate precursor.

Analysis of the product mixture of the reaction reveals that compounds (6.6) and (6.7) are initially formed in approximately equimolar proportions, a consequence, perhaps, of the kinetic control of the reaction. However, the concentration of (6.6) diminishes from 50% to zero between 5 and 20 hours of the reaction. This observation suggests a greater stability of the benzimidate product (6.7) than the phosphorimidate isomer (6.6).

The structure of N-benzoyl-O-ethyl-O,O-dimethylphosphorimidate (6.6) was established according to the following spectroscopic data: as illustrated in Fig. 6.2, the methylene protons of the ethyl group resonate as a low-field quintet ($J_{H,H} = J_{H,P} = 7.5$ Hz), characteristic of the P^{IV}-OCH_2CH_3 function, thus unambiguously establishing the location of the ethyl moiety. The IR spectrum of (6.6) shows an intense carbonyl absorption band at 1611 cm^{-1}. This frequency is 74 cm^{-1} lower than that of the N-benzoyl precursor (1a) and is consistent with the Π,Π-conjugation existing within the O=C-N=P moiety[18] of the phosphorimidate (6.6). In addition, a new band is observed at 1347 cm^{-1} owing to the presence of a P=N bond. The positions of these two prominent absorptions are in excellent agreement with the $\nu_{C=O}$ and $\nu_{P=N}$ frequencies observed for a number of other N-acyl trialkylphosphorimidates[149c,e] (1608 - 1620 cm^{-1} and 1346 - 1380 cm^{-1} respectively).

In contrast to (6.6), the methylene protons of (6.7) resonate as a quartet ($J_{H,H} = 7.5$ Hz) indicating no coupling with the ^{31}P nucleus. Analysis of the IR spectrum of (6.7) revealed the absence of a carbonyl absorption, but retention of a phosphoryl absorption, at 1271 cm^{-1} accompanied by the appearance of a prominent new absorption at 1657 cm^{-1}, characteristic of an imidate C=N bond.[151]

In an attempt to effect N-alkylation of (6.5), a second anhydrous alkylation procedure modelled on that described by Zwierzak[28] was employed.

6.2.2 ETHYLATION WITH ETHYL IODIDE IN THE PRESENCE OF A PHASE TRANSFER CATALYST

Zwierzak[28] has recently discussed the synthetic utility of the urethane sodium salt (6.8) as a superior substitute for potassium phthalimide in

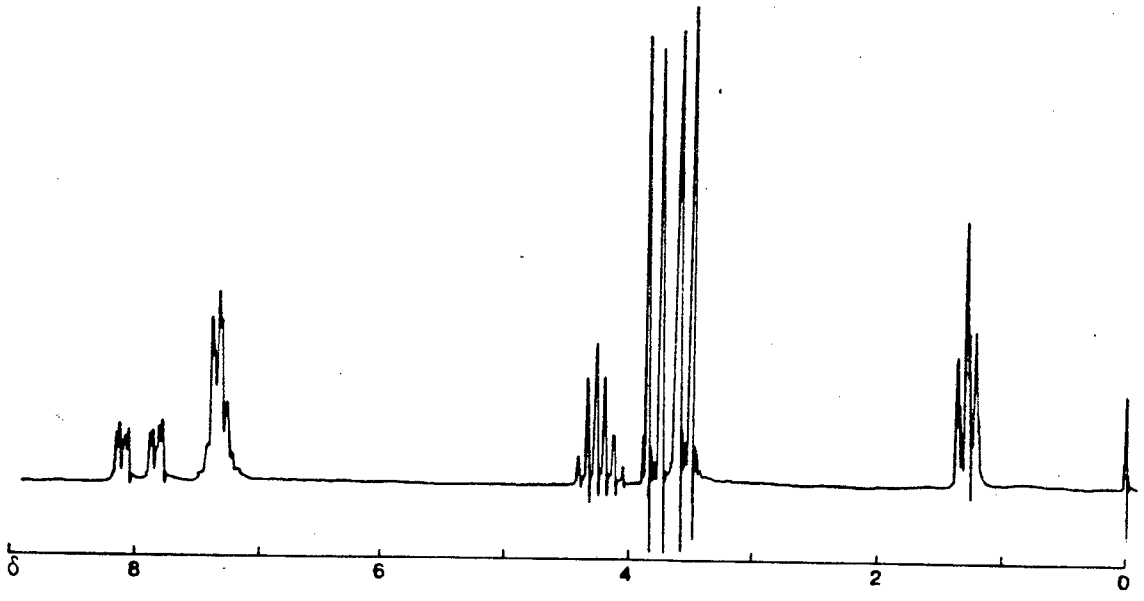


Figure 6.1 ^{1}H NMR spectrum of the product mixture of the triethyloxonium ion ethylation of (6.5).

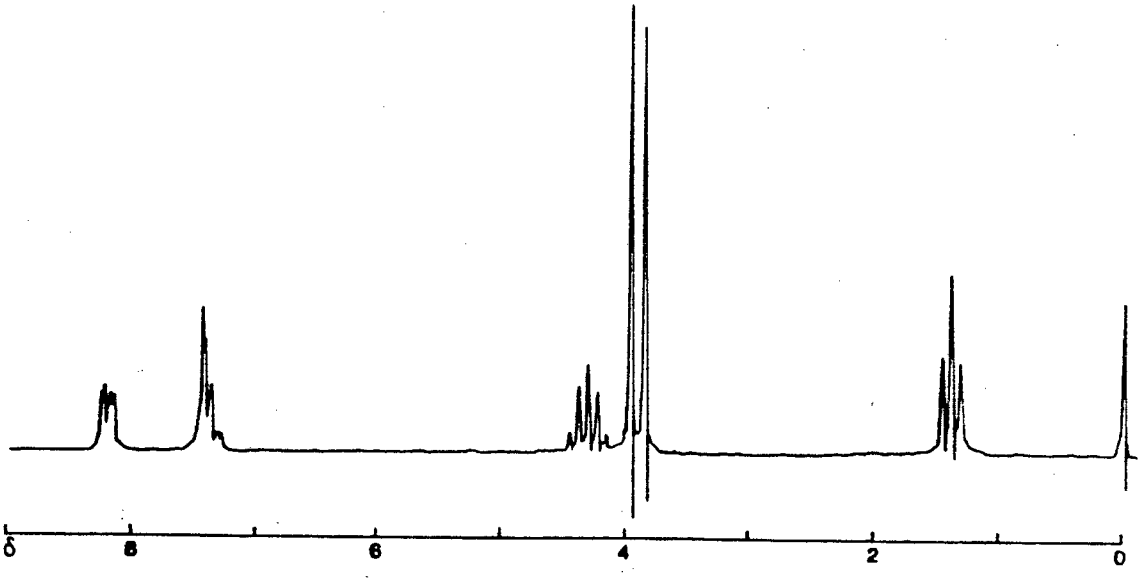
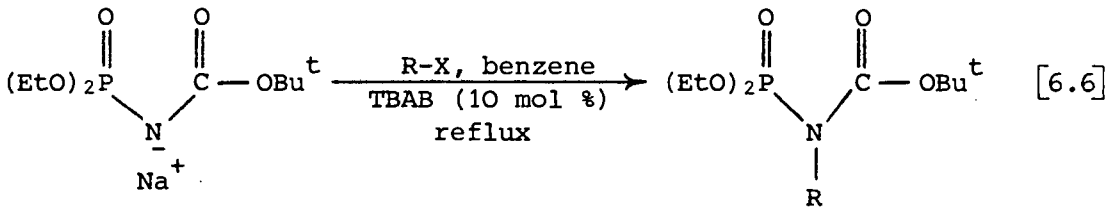


Figure 6.2 ^{1}H NMR spectrum of (6.6).

the Gabriel synthesis of amines. It has been found that under the reaction conditions shown in eq. 6.6, exclusive N-alkylation occurs giving (6.9) which is readily doubly de-protected to yield the free primary amine RNH_2. The reaction is carried out in the presence of a catalytic amount of the phase transfer catalyst, tetra-n-butylammonium bromide (TBAB):



[6.6]

(6.8) (6.9)

The technique of solid-liquid phase transfer catalysis has been extensively applied in facilitating nucleophilic substitution reactions involving bulky, "soft" anions.[152] The function of the catalyst under such conditions is obviously one of ion exchange and subsequent nucleophilic enhancement of the anion.

The reaction of the sodium salt (6.5) with ethyl iodide was carried out under similar conditions, with a view to achieving N-ethylation. However, the absence of the characteristic P(O)NEt signals in the ^1H NMR spectrum of the product mixture, indicates that despite the structural resemblance to (6.8), the analogous N-ethylation of (6.5) does not occur. The product mixture was found to consist of two compounds having extremely similar R_f values on a TLC plate and as illustrated in Fig. 6.3, a close relationship between the compounds is inferred from the ^1H NMR spectrum of the product mixture. Both compounds exhibit a quartet at δ4.0 - 4.5, characteristic of the methylene protons of an ethyl group not coupled to a ^{31}P nucleus. The spectrum of product A is identical to that of the benzimidate (6.7) prepared above and, in view of the great similarity in the spectral characteristics of products A and B (Fig. 6.3), it would appear that they are the

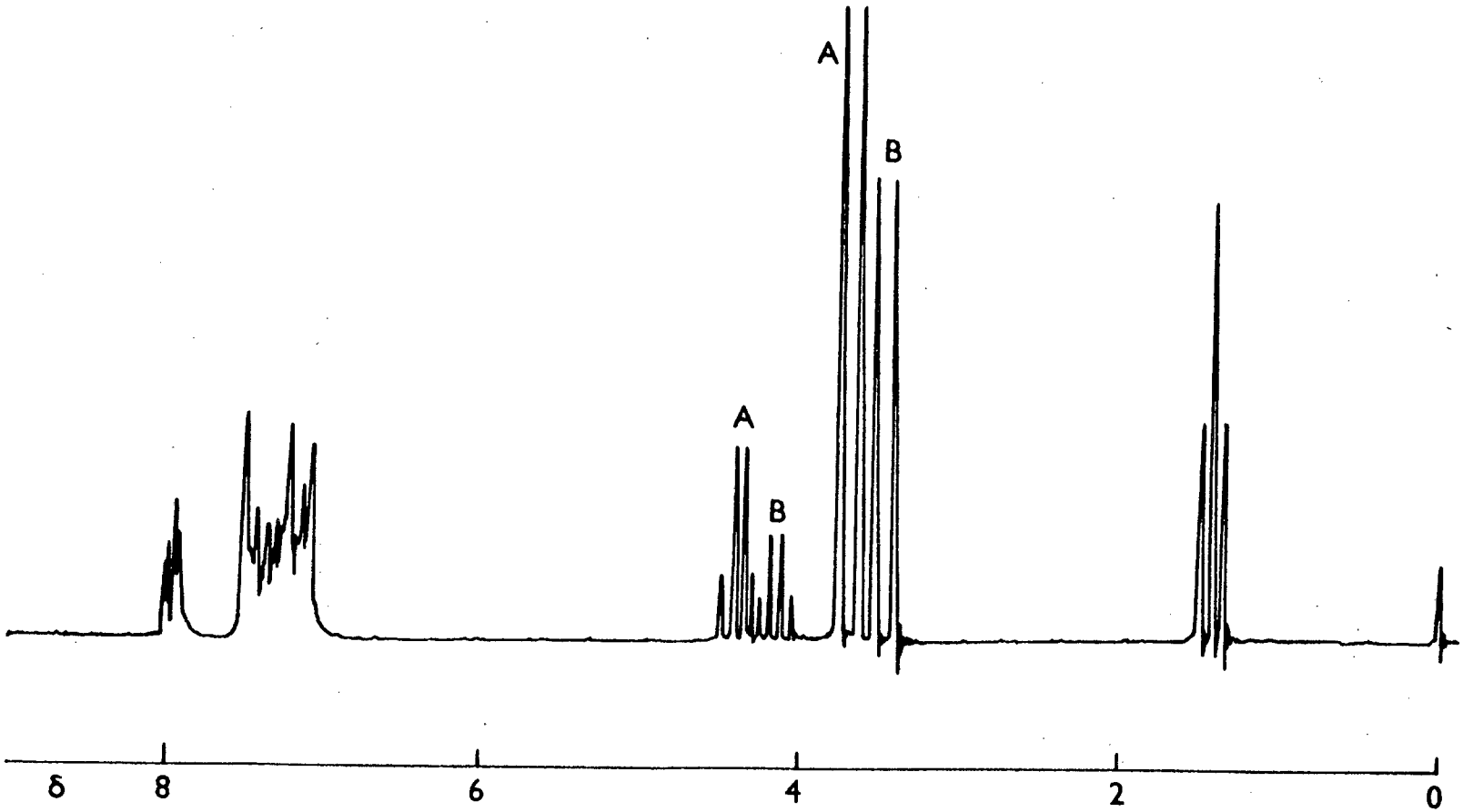
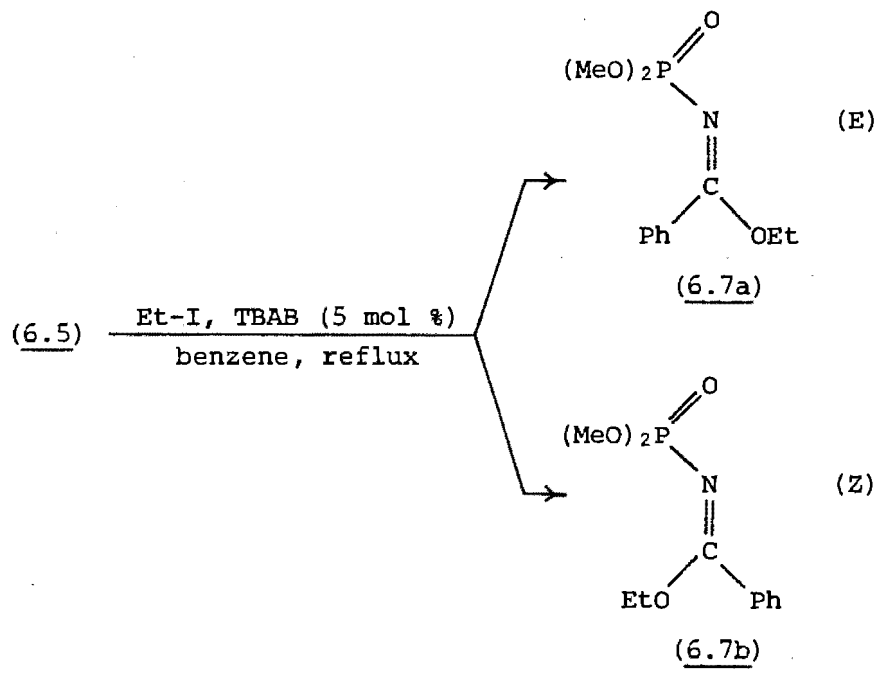


Figure 6.3 ^{1}H NMR spectrum of the product mixture of the phase transfer-catalysed ethyl iodide ethylation of (6.5).

E/Z geometrical isomers of O-ethyl-N-(dimethylphosphoryl) benzimidate, (6.7a) and (6.7b) respectively:



[6.7]

The benzimidates were separated by column chromatography and their structures determined by ^{1}H and ^{13}C NMR, IR and mass spectrometry.

The ^{13}C NMR spectra of the individual compounds are very similar, both showing five low-field signals of the sp^2 carbon atoms (four aromatic and one of the C=N group), one high-field signal of the β-methyl carbon of the ethyl group and two mid-field signals: a doublet ($J_{C,P}$ = 7.0 Hz) of the dimethylphosphoryl methyl groups and a singlet of the OCH_2 group of the O-imidate function. The most obvious difference between the ^{13}C NMR spectra of the two compounds lies in the chemical shift of the latter signal with that of A occurring approximately 20 Hz downfield from the corresponding signal of B. Since the α-methylene carbons of (6.7a) and (6.7b) differ significantly in through-space distance to the phosphoryl group and to the pair of non-bonding electrons on nitrogen (E/Z relation), large differences in the shielding parameters of these atoms are expected. The IR spectra of the individual products are very similar, as anticipated from geometrical isomers,[153] with both containing a prominent phosphoryl absorption at

1268 - 1271 cm^{-1} and a characteristic $\nu_{C=N}$ absorption at 1654 - 1657 cm^{-1}, in good agreement with the available literature values.

The NMR and IR spectroscopic results thus fully confirm the suggestion of geometrical isomerism. It was found that a detailed comparative analysis of their mass spectra provided a means of unambiguous assignment of E/Z geometry to the individual products. The mass spectra of the geometrical isomers and their positional isomer (6.6) were recorded and the fragmentation patterns of each of the isomers have been elucidated. The main ions observed are listed in Table 6.1.

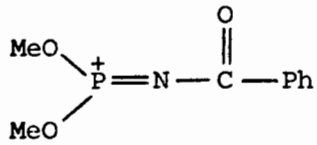
The principal fragmentation pathway of (6.6) involves loss of a phenyl radical to give the resonance-stabilised ion of m/e 180, as shown in Scheme 6.4. Subsequent loss of ethylene via a McLafferty rearrangement gives rise to the base peak of m/e 152, which can then fragment as indicated. It is unlikely that the loss of 28 mass units in going from m/e 180 to m/e 152 is due to expulsion of CO since the resulting ion would be of much lower stability. The molecular ion also undergoes homolytic N-C bond fission to give the stable benzoylium ion of m/e 105 which further fragments in the characteristic way. Two metastable-supported pathways of minor importance involve loss of ethylene and water from the molecular ion to give fragments of m/e 229 and 239 respectively. The fragments of m/e 212, 154, 127 and 103 can be accounted for by an initial rearrangement of the molecular ion, involving intramolecular nucleophilic attack by carbonyl oxygen at phosphorus to give a tbp intermediate which may collapse by loss of ethoxy radical to m/e 212, by loss of benzonitrile to the mixed phosphate ester of m/e 154, or by loss of a neutral molecule of the phosphate ester to yield benzonitrile radical ion of m/e 103. Loss of vinyl radical from m/e 154 via a double hydrogen shift mechanism (Chapter 5) yields the stable quasiphosphonium ion of m/e 127.

An alternative explanation of the presence of fragments of m/e 154 and 127 is based upon the observation of Kirsanov *et al.*[149a,b] that N-acyl triarylphosphorimidates (6.10) thermally disproportionate to release a nitrile and triarylphosphate:

$$(ArO)_3P{=}N{-}\overset{\overset{O}{\|}}{C}{-}R \xrightarrow{\Delta} O{=}P(OAr)_3 + RCN \qquad [6.8]$$

(6.10)

No mechanism was proposed for this reaction, but the most likely intermediate is analogous to that shown in Scheme 6.4. In light of the above, it is conceivable that ethyldimethylphosphate and benzonitrile are formed prior to entering the ionisation chamber. The ion of m/e 212 could be accounted for by direct loss of ethoxy radical from the molecular ion to yield fragment (6.11) which is a nitrogen analogue of a phosphorylium ion:



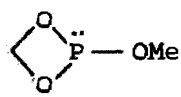
(6.11)

Since no experiments were conducted to establish whether the substrate isomerisation and subsequent collapse to a nitrile and phosphate ester is of thermal or electron impact-induced origin, both possibilities remain feasible. However, irrespective of its origin, the isomerisation reaction *per se* is of great interest, since it involves intramolecular nucleophilic attack by a carbonyl oxygen atom at a phosphorimidate P^{IV} centre and is thus analogous to the previously discussed rearrangement reaction of N-acyl phosphoramidates, for which mass spectral (Chapter 5) and structural (Chapter 4) evidence exist. As in the Wittig and related reactions, intramolecular rearrangements of this type are largely inspired by the great affinity of phosphorus for oxygen.

Very little information is available on the mass spectral characteristics of N-substituted phosphorimidates. Goldwhite *et al.*[76b] have discussed the possible origin of the most significant ions in the mass spectra of $(RO)_3P{=}NEt$ (R = Me, Et) and comparison with the mass spectrum of (6.6) shows that the mode of fragmentation is determined by the substituent at nitrogen rather than the substituents at phosphorus.

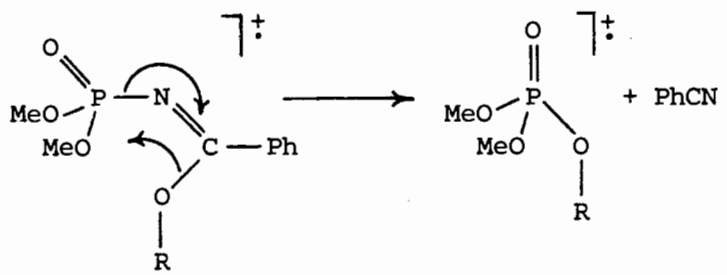
The most important fragmentation pathways available to the geometrical isomers (6.7a) and (6.7b) are given in Scheme 6.5. As can be seen from Table 6.1, the mass spectra are specific for the type of isomer (E vs. Z), not in the nature of the ions, but in their relative abundance.

The two principal fragmentation pathways both involve the migration of a hydrogen atom from either the methoxyl or ethoxyl group to the nitrogen atom (pathways a, b). In the E isomer (6.7a), loss of ethylene via a McLafferty rearrangement is the most favoured pathway yielding the radical ion m/e 229 (pathway a). This species is N-benzoyl dimethylphosphoramidate, the precursor of the sodium salt (6.5) and its mass spectrum has been discussed above (Chapter 5). The second important H-migration fragmentation involves expulsion of a molecule of $C_2H_5O_3P$ and formation of O-ethylbenzimidate radical ion m/e 149 (pathway b). Expulsion of the same neutral molecule has also been observed from $(MeO)_2P(O)NHPh]^{+\bullet}$ and although the relevant fragmentation pathways are not metastable-supported, this neutral species may be speculatively identified as methyl methylene phosphite,



The mass spectrum of independently synthesised ethyl benzimidate was recorded and the molecular ion found to be remarkably stable (base peak). However, isomerisation to N-ethylbenzamide does take place and subsequent fragmentation occurs as expected.[108]

Loss of ethoxy radical from the molecular ion to yield N-dimethylphosphoryl benzonitrilium ion m/e 212 is a third minor pathway common to both isomers (pathway e). Loss of hydrogen from the molecular ion to yield the O-vinyl derivative m/e 255 is another minor pathway, again common to both isomers (pathway c). However, loss of benzonitrile from the molecular ion and from m/e 255 to yield the mixed phosphate esters m/e 154 and 152 respectively (pathways d, f) is more predominant in the fragmentation pattern of the Z isomer (6.7b) than the E isomer (6.7a). This is reasonable, since loss of benzonitrile from such a parent ion requires a *cis* orientation of the N-dimethylphosphoryl substituent and the migrating O-alkyl group (eq. 6.9):



[6.9]

R = Et (m/e 257)

R = $CH{=}CH_2$ (m/e 255)

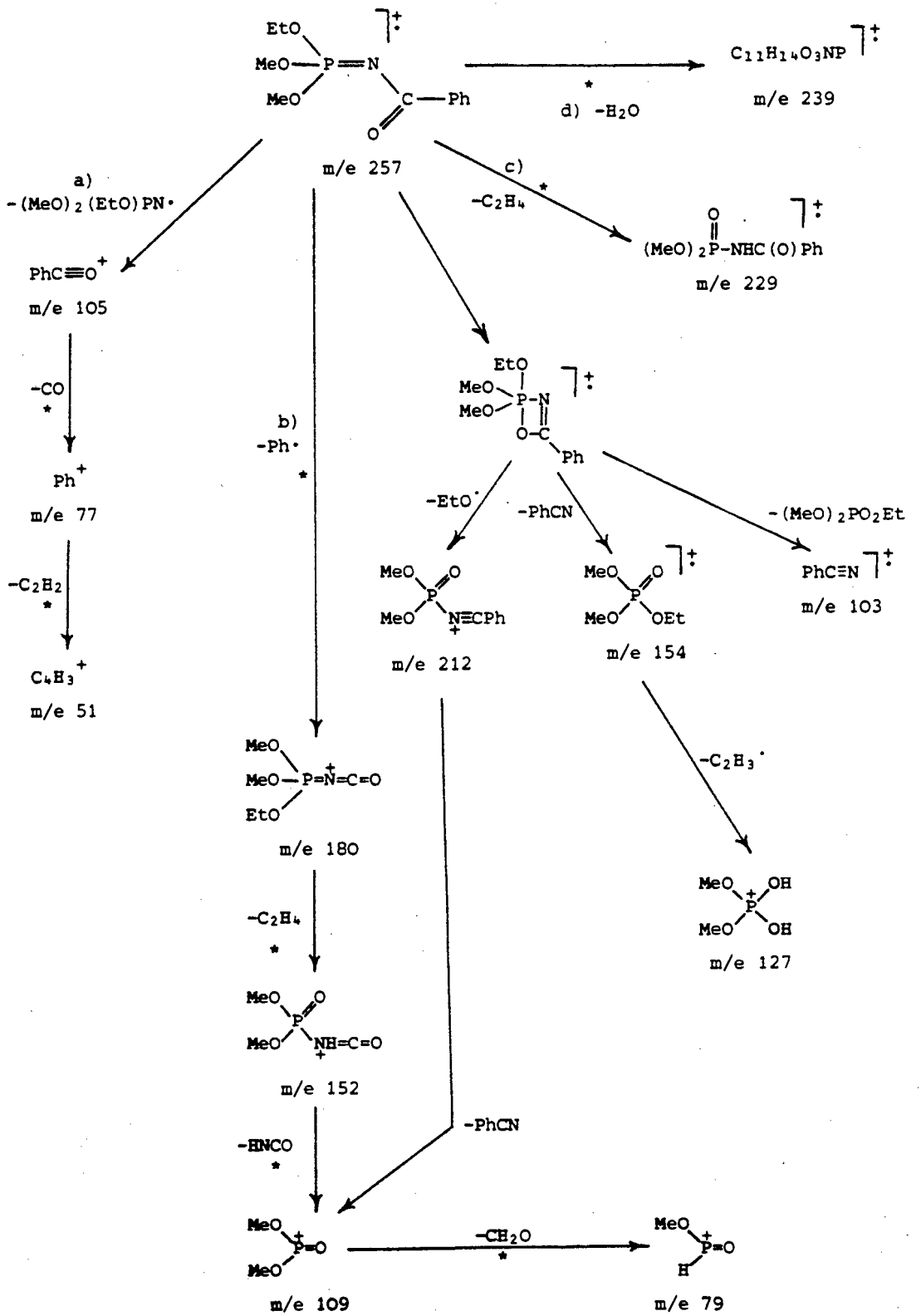
Mixed phosphate ester formation appears to be the best explanation for the peaks observed at m/e 110, 121 and 127.

The main difference in the mass spectra of the geometrical isomers is a consequence of the stereospecificity of pathways a, d and f, the former requiring a *trans* orientation and the latter two requiring a *cis* orientation of the N-dimethylphosphoryl and O-ethyl groups. The observation that all peaks are common to both spectra, but the peaks arising from initial loss of ethylene from the molecular ion (m/e 229, 228, 201, 105, 77 and 51) are noticeably more abundant in the mass spectrum of (6.7a) than (6.7b), indicates a certain degree of interconversion of the isomers prior to fragmentation. The ion source temperature of 200°C thus appears to be sufficiently high to

Table 6.1 Main ions in the mass spectra of the ethylation products.

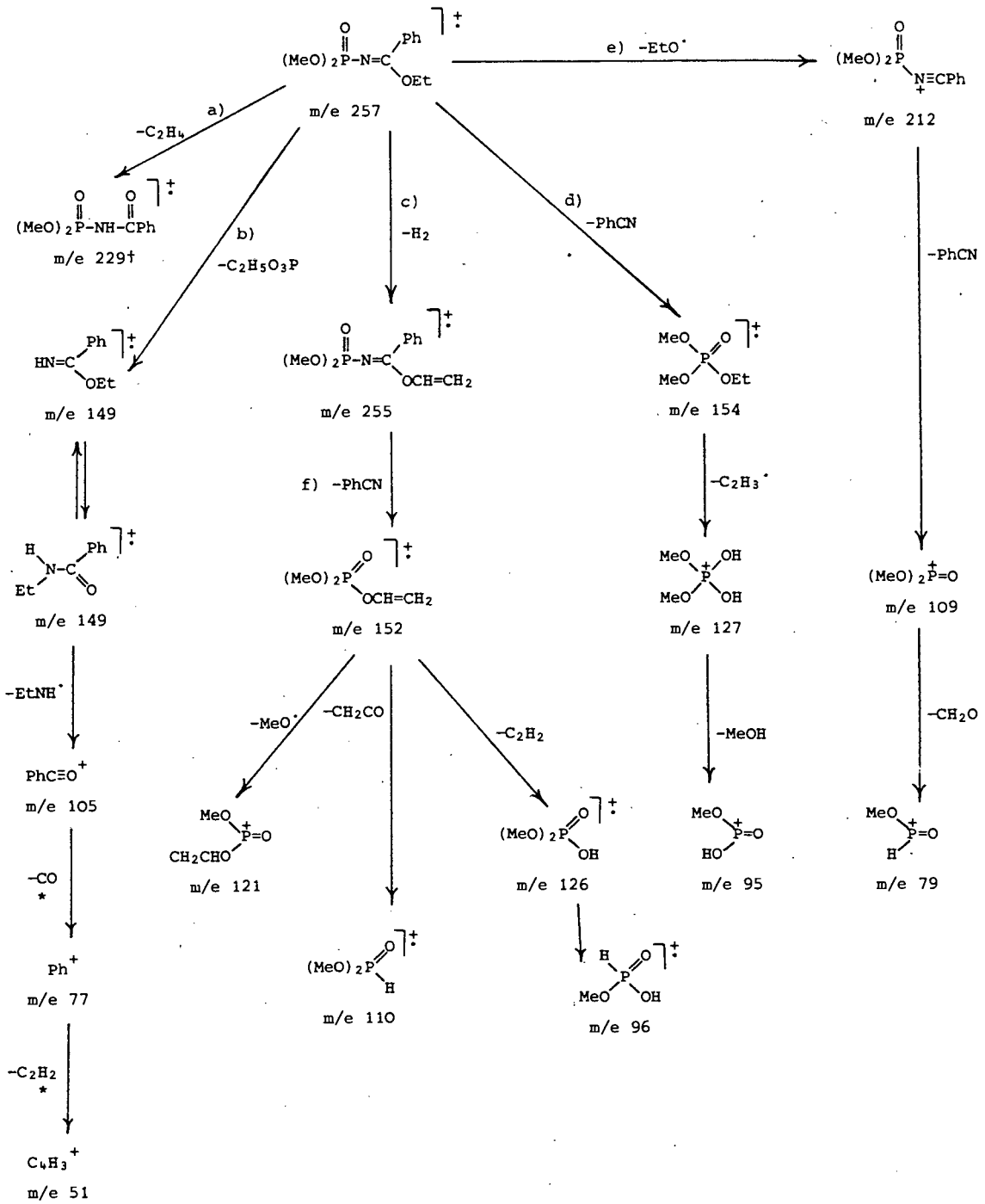
m/e	(6.6) Relative Intensity	(6.7a) Relative Intensity	(6.7b) Relative Intensity
mol. ion	4	2	6
41	-	10	-
47	-	4	-
51	10	27	17
77	14	75	31
78	-	13	8
79	7	6	9
80	-	-	9
95	-	8	10
96	7	10	7
103	8	9	11
104	-	12	31
105	15	100	50
106	-	13	5
109	28	20	41
110	-	32	57
118	-	12	14
121	7	8	5
126	-	10	30
127	10	6	15
131	-	8	11
149	-	55	100
152	100	20	47
154	6	3	6
180	44	-	-
201	-	7	-
212	10	15	21
228	-	3	-
229	5	14	8
239	5	-	-
255	-	12	19

Scheme 6.4 Proposed fragmentation pattern of (6.6).[a]



[a]Pathways supported by metastable peaks are indicated by an asterisk.

Scheme 6.5 Proposed fragmentation pattern of (6.7a) and (6.7b).



† Radical ion m/e 229 further fragments to give species of m/e 228, 201, 152, 126, 105, 77 and 51.

cause rotation about the carbon-nitrogen bond. The value of the C-N rotational barrier in the benzimidates (6.7) is not known; however, it should not differ significantly from that determined for other N-substituted O-alkyl imidates. Meese *et al.*[154] have used dynamic NMR spectroscopy to determine the inversion barriers in a series of O-alkyl imidates and report $\Delta G^{\ddagger}_{E\rightarrow Z}$ and $\Delta G^{\ddagger}_{Z\rightarrow E}$ values of the order of 67 - 88 kJ mol^{-1}.[155] Such inversion barriers are sufficiently low to enable E⇌Z interconversion at the ion source temperature employed to record the mass spectra of (6.7a,b).[157]

A conclusion drawn from this study is that mass spectrometry is clearly a useful tool for distinguishing positional isomers. However, in accordance with the observation made by Natalis,[158] a more detailed analysis of comparative ion peak intensities is required when using this technique to differentiate geometrical isomers. An indication of the negative charge distribution within the OPNCO moiety of the anion is obtainable from comparative IR spectral studies of (6.5) and its precursor (1a) (Table 6.2).

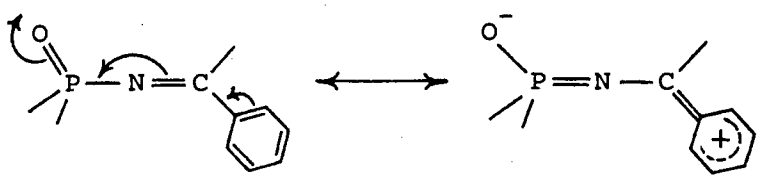
Table 6.2 Comparative IR absorptions of (1a) and (6.5).

Bond	$\nu(cm^{-1})$ (1a)[a]	(6.5)[b]	Δν(%)
P=O	1240	1205	2.9
C=O	1685	1595	5.6

[a] 1% CCl_4 solution; [b] 1% DMSO solution

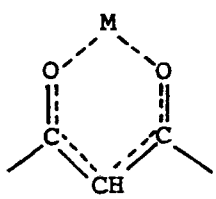
The relative bathochromic shifts of the $\nu_{P=O}$ and $\nu_{C=O}$ absorptions suggest that the extent of carbonyl bond order reduction is almost twice that of the phosphoryl bond order, indicating a greater nucleophilicity of the carbonyl than phosphoryl oxygen atom. Despite this nucleophilicity

difference, the dual orientation of the ethylation reaction of (6.5) with $Et_3O^+BF_4^-$ (eq. 6.3) suggests that both oxygen sites are nonetheless reactive. The gradual room temperature conversion of (6.6) to (6.7) quite clearly demonstrates the strong driving force for regeneration of the P=O bond, even at the expense of replacing the C=O bond by a less favoured C=N bond.[159] An additional factor that lends stability to the isomer (6.7) is the formation of an extensively conjugated system in which the phenyl ring may participate:

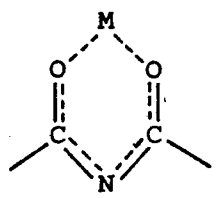


The highly delocalised nature of the anion (6.5) implies a relatively low electron density at the nitrogen atom, which, in conjunction with the relatively hindered position of this nucleophilic centre with respect to the exposed, peripheral carbonyl and phosphoryl oxygen atoms, associates a high activation energy to the N-ethylation process, thus leading to the exclusive formation of the isomers (6.6) and (6.7) under the reaction conditions discussed above (eqs. 6.3, 6.7).

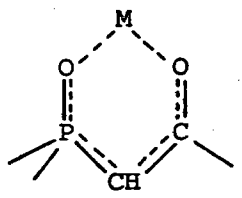
It has been found that the anions derived from acidic β-diketones,[161a] carboxylic imides,[161b] β-ketophosphonates,[161c] and carbamyl methylenephosphonates[161d] form effective chelating agents. The complexation of such ligands with a variety of alkaline, alkaline earth and transition metal ions results in the formation of chelates of the type (6.12 - 6.14), in which the ligand is anchored in a "U-shape".



(6.12)

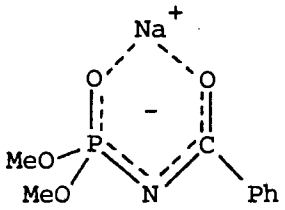


(6.13)

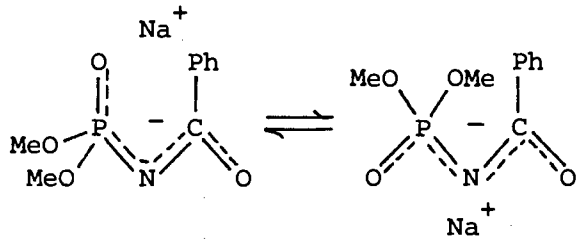


(6.14)

By analogy, the most likely structure of the sodium salt (6.5) is the U-shaped chelate complex (6.5U), with coordination via both the carbonyl and phosphoryl oxygens yielding a tight ion pair and hence lowering the nucleophilic reactivity of the mixed imide anion. Destruction of the chelate complex by rotation about the N-C bond, leads to the formation of the charge-diffuse, loosely bound ion pair (6.5W), in which the ligand may adopt a "W-shape" and exhibit greatly enhanced nucleophilic reactivity.



(6.5U)



(6.5W)

The nature of the ethylation products is determined by the structure of the nucleophile: carbonyl oxygen ethylation of (6.5U) and (6.5W) yields the Z- and E-imidates (6.7b) and (6.7a) respectively, whilst phosphoryl oxygen ethylation of both forms gives rise to the same product (6.6). As illustrated in eq. 6.3, the carbonyl oxygen ethylation of (6.5) with $Et_3O^+BF_4^-$ in dichloromethane at 10 - 15°C yields exclusive formation of the E-isomer (6.7a), indicating the existence of the anion in its reactive W-shape under these conditions. These observations suggest the existence of a U/W equilibrium that is necessarily in favour of the more stable U-shape. However, as a result of the greater reactivity of the less abundant anion towards the ethylating agent, the equilibrium is shifted towards (6.5W), which undergoes phosphoryl and carbonyl oxygen ethylation to yield (6.6) and (6.7a) respectively (eq. 6.10):

$$(6.5U) \rightleftharpoons (6.5W) \xrightarrow[10 - 15°C]{Et_3O^+BF_4^-} (6.6) + (6.7a) \qquad [6.10]$$

Replacement of the sodium counterion by the larger tetrabutylammonium ion bares the anion[161a] and thus enhances the reactivity of both the U and W forms. The formation of approximately equimolar proportions of the E-and Z-imidates (6.7a,b) by ethylation of the anion under the reaction conditions described in eq. 6.7, is indicative of indiscriminate carbonyl oxygen ethylation of the U-and W-shaped anions at the temperature employed (80°C) (eq. 6.11):

$$(6.7b) \xleftarrow{EtI} U \underset{}{\overset{\Delta,\ TBAB}{\rightleftharpoons}} W \xrightarrow{EtI} (6.7a) \qquad [6.11]$$

This study has revealed that the nucleophilic behaviour of the mixed imide system under basic conditions, bears little resemblance to that of the respective parent amide systems, as a consequence of the effective elimination of the nitrogen atom as a competitive nucleophilic site. Therefore, the possibility of utilising N-alkylation of the accessible secondary mixed imides as a synthetic route to the less accessible tertiary derivatives, is ruled out.

In addition, the observed difference in the nucleophilic behaviour of (6.5) and the related imidic substrate (6.8) under ostensibly identical conditions,[28] suggests that the kinetic and thermodynamic factors governing the nucleophilic reactivity of the phosphoric-carboxylic imide system, are a sensitive function of the substrate structure.

CHAPTER 7

Solvolytic Behaviour

7.1 INTRODUCTION

There are two important factors governing the selectivity of the nucleophilic cleavage reactions of mixed diacyl systems, such as anhydrides and imides, which are structurally derived from two different acids:

(i) the relative electrophilicities of the two acyl centres, and

(ii) the extent of leaving group departure in the rate-determining transition state.

Since nucleophilic substitution at a carbonyl centre generally proceeds via rate-determining tetrahedral intermediate formation, factor (i) predominates in directing nucleophilic attack at mixed carboxylic anhydrides. In contrast, the leaving group ability plays an important role in phosphorylation processes and determines the orientation of nucleophilic substitution in unsymmetrical pyrophosphates.[162] The structural dependence of the solvolytic reactivity of mixed phosphoric-carboxylic systems is thus additionally complicated by the mechanistic differences that exist between the two possible nucleophilic displacement reactions.

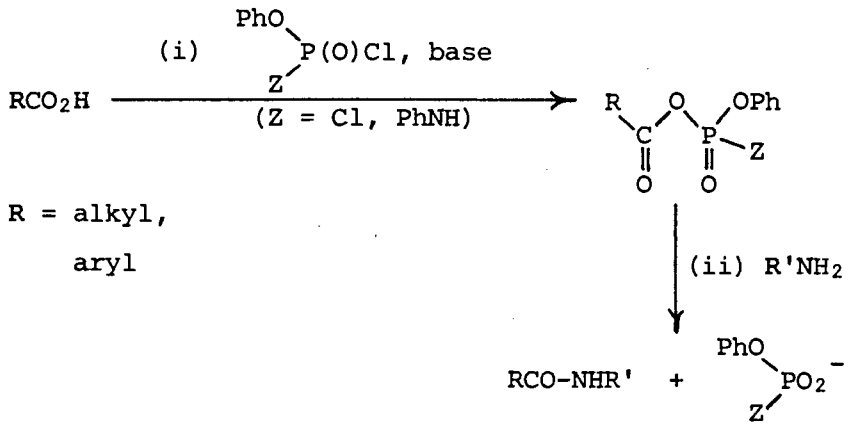
The neutral solvolysis of acyclic mixed phosphoric-carboxylic[163,164] and phosphoric-carbonic[165] anhydrides (7.1) by both oxygen[164,165] and nitrogen[163] nucleophiles, has been the subject of a great many investigations and is well established. The regiospecific attack by oxygen and nitrogen nucleophiles at the carbonyl centre of (7.1) is consistent with the poor leaving ability of a carboxylate group disfavouring attack at phosphorus, as opposed to the strong electron-withdrawing ability of a dialkylphosphoryloxy substituent[166] facilitating attack at carbon (eq. 7.1):

$$(RO)_2P(O)\text{-}O\text{-}C(O)X + NuH \longrightarrow (RO)_2PO_2H + Nu\text{-}C(O)X \qquad [7.1]$$

(7.1)

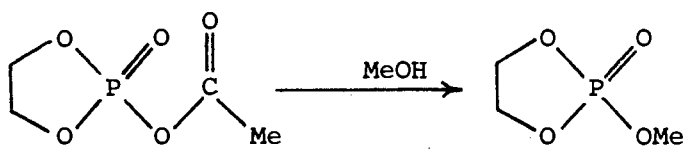
X = R', OR'

Owing to their "activated" carboxylic acid solvolytic behaviour, the mixed anhydride reagents (7.1) have acquired an established position in peptide synthesis.[167] Mixed anhydride generation can conveniently take place *in situ*, providing a method of facile and high-yield amide formation (eq. 7.2):[168]



[7.2]

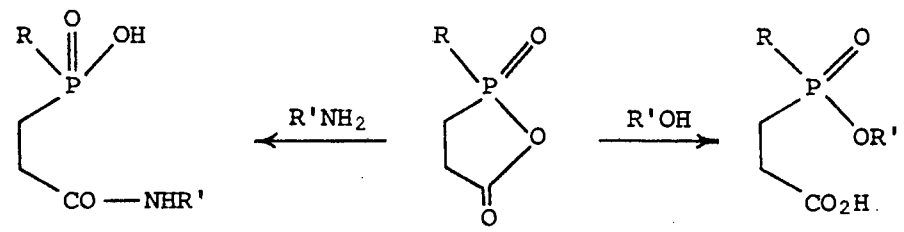
Kluger and Wasserstein[169] have shown that incorporation of the phosphorus atom into a five-membered ring reverses the regioselectivity as a result of the enhanced reactivity of cyclic phosphates relative to their acyclic analogues (eq. 7.3):[170]



[7.3]

(7.2)

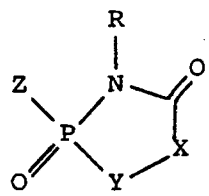
The phosphinic-carboxylic anhydrides have received less attention than their phosphoric analogues. However, the cyclic derivative (7.3) shows an interesting regiospecificity change depending upon the nucleophile: aminolysis occurs via carbonyl attack, whereas alcoholysis favours P-O bond formation (eq. 7.4):[167]



[7.4]

(7.3)

The solvolytic behaviour of the mixed imide system (1) must be related to that of its parent amides. Although carboxamide and phosphylamide systems are stable in neutral solution, they exhibit markedly different nitrogen-acyl reactivity under acidic conditions. Carboxamides undergo slow acidic solvolysis via tetrahedral intermediate formation, by solvent attack on the oxygen-protonated form of the substrate conjugate acid ($A_o^{T_2}$ mechanism).[171] Phosphylamides, on the other hand, are extremely reactive in acidic media, owing to the participation of an $S_N2(P)$ mechanism, in which the amine leaving group is directly displaced by solvent from the nitrogen-protonated conjugate acid.[13] The neutral solvolysis of the P(O)-N bond of a mixed imide is likely to proceed via a pentacoordinate intermediate, owing to the weak nucleofugality of the carboxamide group and the low nucleophilicity of the solvent (e.g. water, alcohol).[172] Since N-C(O) solvolysis necessarily proceeds via an analogous tetrahedral intermediate, the orientation of nucleophilic attack under neutral conditions should be directly dependent upon the relative electrophilicities of the P=O and C=O centres. Mulliez[173] has found that the cyclic N-acyl phosphylamides (7.4) undergo exclusive P(O)-N hydrolysis and alcoholysis. In contrast, amine nucleophiles attack the more strongly electrophilic α-carbonyl centre of (7.4b), whilst (7.4a,c) remain unsusceptible to aminolysis.



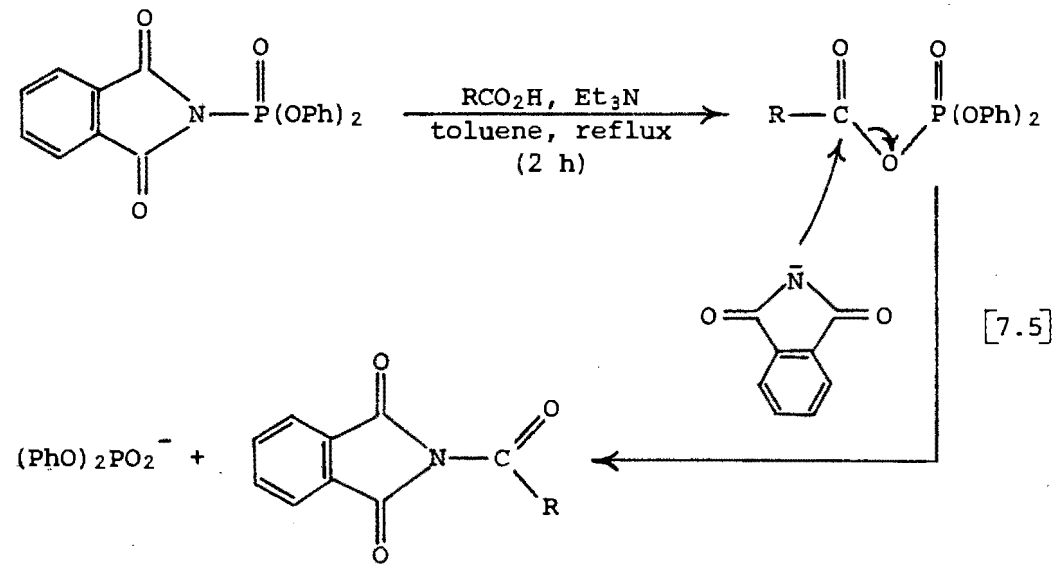
(7.4)

a, X = Y = CH_2

b, X = CO, Y = NR

c, X = CH_2, Y = NR'

The regioselectivity of the reaction of (7.4) with SOH (S = H, alkyl) has been explained in terms of weak carbonyl carbon electrophilicity in (7.4a,c) (as a result of strong N-C(O) conjugation) and the high reactivity of five-membered cyclic phosphoric amides and esters with nucleophiles having strongly apicophilic conjugate bases, via an addition-elimination mechanism.[173b] Palomo[174] has recently found that carboxylate nucleophiles regiospecifically attack the phosphoryl centre of N-diphenylphosphoryl phthalimide to generate a mixed phosphoric-carboxylic anhydride. The mixed anhydride undergoes subsequent reaction by exclusive attack of phthalimide ion at the carbonyl centre (c.f. eq. 7.1), to yield the corresponding N-acyl phthalimide (eq. 7.5):



[7.5]

Since the protonation behaviour of the mixed imide system (1) is complicated by virtue of its tribasic nature (nitrogen, carbonyl and phosphyl oxygens), predictions concerning its acidic solvolysis are difficult. The protonation equilibria responsible for activating the respective nitrogen-acyl bonds towards solvolysis are expected to respond differently to the effects introduced by the second N-acyl group. The carbonyl oxygen basicity should not be significantly reduced by N-phosphylation.[175] However, nucleophilic approach to the carbonyl centre of the corresponding conjugate acid would be

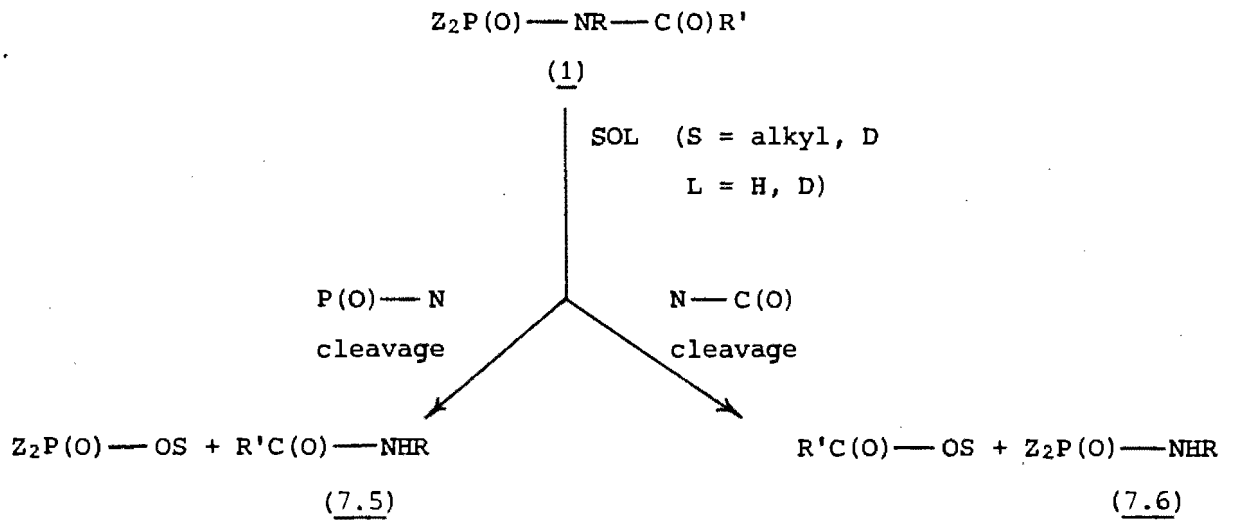
facilitated by the relatively enhanced carbonyl carbon electrophilicity.[171] In contrast, introduction of an N-carboxyacyl substituent would probably severely suppress the N-protonation that is necessary to effect facile phosphylamide solvolysis. In their work on the acidic hydrolysis[24c] in 1.0 - 11.5 M $HClO_4$ and ethanolysis[25] in 2.5 M HCl of N-benzoylphosphoramidic acid, Halmann *et al.* have indeed found that although this substrate acts as an exclusive phosphorylating (vs. benzoylating) agent, the solvolysis process is remarkably unsusceptible to acid catalysis. Parallel behaviour is also exhibited by N-sulfonyl and N-phosphoryl phosphoramidic acids[24d,176] and has been attributed to the weak nitrogen atom basicity of $X\text{-}NH\text{-}PO(OH)_2$ ($X = RCO$, $ArSO_2$, $(RO)_2PO$) and subsequent low concentration of the reactive N-protonated species.[24d,25,176]

A kinetic study of the neutral and acid-catalysed solvolysis of selected mixed imides (1) was therefore carried out with the primary aim of quantifying the response of each of the N-acyl functions to the structural modification involved in going from the individual amide systems to the corresponding mixed system.

7.2 NEUTRAL SOLVOLYSIS

The reactivity of selected mixed imides towards alcoholysis and hydrolysis under neutral conditions was investigated. The two solvolytic pathways available to such a system are illustrated in Scheme 7.1.

Scheme 7.1 Neutral solvolysis.



7.2.1 ALCOHOLYSIS

The reaction of (1c) with excess alcohol ROH (R = Me, Et) at 25°C was followed by gas chromatography (GC). The retention times of all possible carboxylic and phosphoric amide and ester products are listed in Table 7.1. Product identification and hence, determination of the alcoholysis orientation, was accomplished by spiking the reaction mixture with genuine amide and ester samples. Both methanolysis and ethanolysis of (1c) were thus found to proceed with exclusive P(O)—N cleavage. Under the experimental

Table 7.1 Retention times (t_R, min.) of alcoholysis products of (1c).

Substrate	t_R	Substrate	t_R
(1c)	9.1	$MeCO_2Et$	*a*
MeCONHMe	3.8	$(MeO)_3PO$	3.2
$(MeO)_2PONHMe$	8.4	$(MeO)_2PO_2Et$	3.6
$MeCO_2Me$	*a*		

[a]Substrate peak masked by solvent (alcohol).

high substrate concentration (*ca.* 0.2 - 0.3 M). This necessitates the use of extremely high buffer concentrations for reactions involving the generation of acidic products. The reactions of (1c-g) with D_2O at 25°C were therefore carried out in the absence of buffer. The hydrolytic behaviour of these substrates is varied and covers an extremely wide reactivity range.

The phosphinic derivative (1f) was found to be the only tertiary substrate that is indefinitely stable in D_2O solution at 25°C. The N-benzoyl substrate (1e) undergoes exclusive P(O)-N cleavage, as indicated by the simultaneous appearance and disappearance of N-methylbenzamide and substrate respectively, with the hydrolysis reaction complete in 24 days. The extremely hygroscopic cyclic substrate (1g) shows the greatest hydrolytic instability under these conditions. The reaction at 25°C is complete within 7 mins.; ^1H NMR spectroscopic analysis of the final product mixture revealed that the hydrolysis reaction proceeds with exclusive attack at phosphorus. The most interesting hydrolytic behaviour is, however, exhibited by the substrates (1c,d). Both substrates exhibit qualitatively identical hydrolysis patterns, consisting of two distinct steps:

1. Initial exclusive P(O)-N hydrolysis, as indicated by the appearance of N-methylacetamide.
2. After approximately 5% conversion of the substrate to dialkylphosphoric acid and N-methylacetamide, the simultaneous formation of acetic acid and methylammonium ion commences and proceeds at a steadily increasing rate.

The variation in the concentrations of (1d) and its hydrolysis products, as a function of time, is illustrated in Fig. 7.1. The dialkylphosphoric acid liberated in step 1 causes a progressive reduction in the pD of the medium. If the initial substrate concentration is 0.28 M, 5% reaction results in an increase in the acidity of the medium to a pD value of

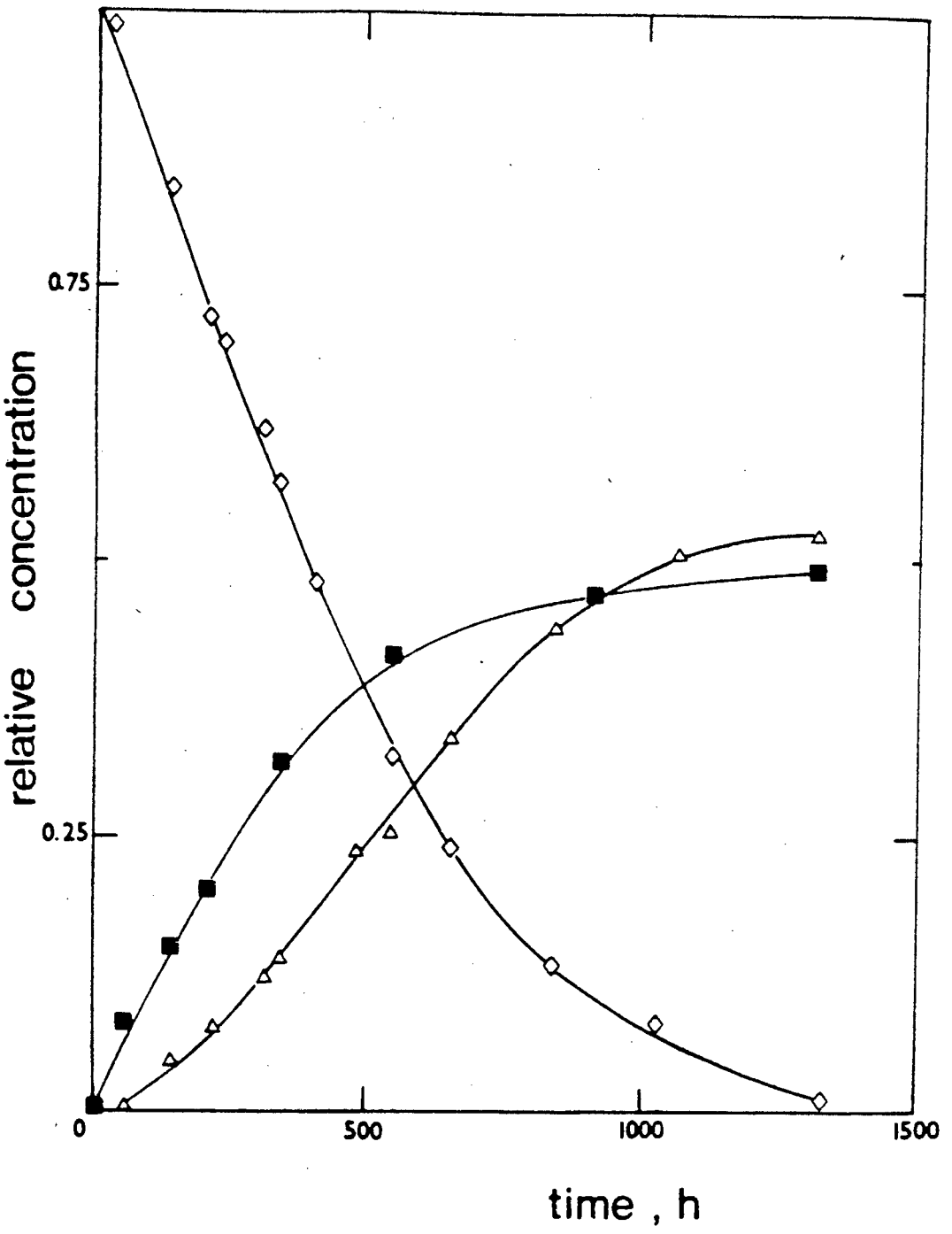


Figure 7.1 The concentration-time plots for the substrate and products in the reaction of (1d) (0.20 M) with D_2O at 25°C: (1d), —◇—; P-N cleavage product (MeCONDMe), —■—; N-C cleavage products ($MeCO_2D$, MeN^+D_3), —△—.

approximately 2.[177] At this stage, the medium is apparently sufficiently acidic to effect acid-catalysed N-C(O) hydrolysis, which liberates acetic acid and N-methyl dialkylphosphoramidate. However, the latter does not appear to accumulate in the medium, as indicated by the absence of a characteristic N-methyl doublet (J(PNCH) 12 Hz) in the spectrum of the reaction mixture; owing to its extreme acid lability, rapid hydrolysis ensues, accounting for the concurrent growth of methylammonium ion and acetic acid. The amidate (7.6) therefore behaves as a "steady state" species under these conditions. A comparison of the concentration-time plots of N-methylacetamide and methylammonium ion/acetic acid (Fig. 7.1) indicates a significantly different response of the P(O)-N and N-C(O) hydrolyses of (1d) to increasing medium acidity, with the latter seemingly more susceptible to autocatalysis than the former.

The stability of the N-C(O) bond of (1c) in neutral alcohol and of (1f) in D_2O supports the proposal that acid catalysis is a pre-requisite for mixed imide N-C(O) solvolysis since, in the former case, all the alcoholysis products are neutral and in the latter, the absence of initial P(O)-N hydrolysis precludes the possibility of acid catalysis. The absence of N-C(O) cleavage of (1e), despite the accumulation of acid in the medium caused by P(O)-N cleavage, indicates a greater stability of an N-C(O)Ph than N-C(O)Me linkage in a mixed imide system. This observation is consistent with the lower basicity of an N-substituted benzamide than its acetamide analogue ($\Delta pK_a \cong -1$),[179] resulting in a relatively slow rate of acid-catalysed N-C(O)Ph hydrolysis.[180]

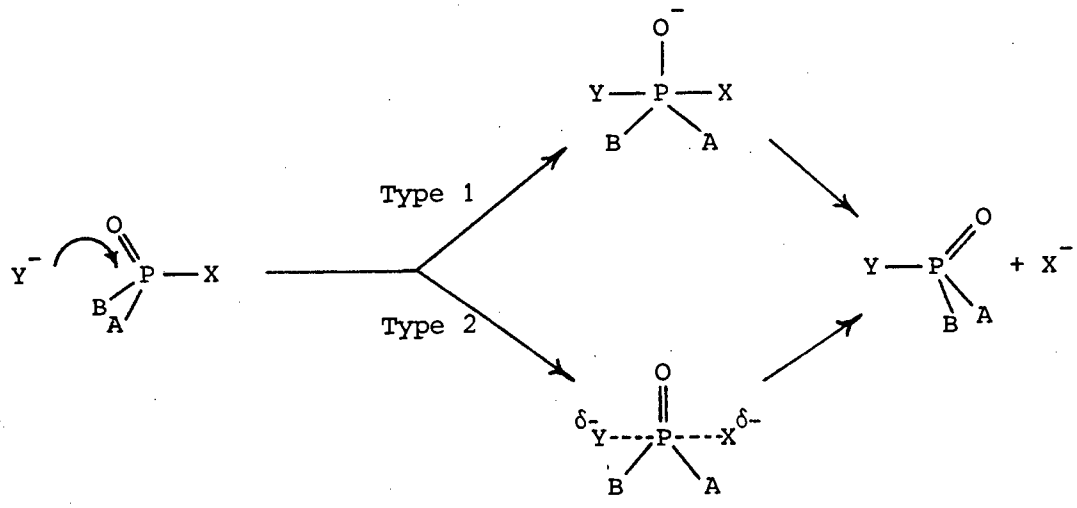
Finally, in contrast to the hydrolytic instability demonstrated by the tertiary N-benzoyl substrate (1e), the secondary analogues (1a,b) are found to be indefinitely stable in aqueous solution at 25°C.[183]

7.2.3 MECHANISM OF NEUTRAL P(O)-N SOLVOLYSIS

It is apparent from the above argument that the solvolytic pathway of interest under neutral conditions, involves P(O)-N cleavage. The mechanisms of bimolecular nucleophilic displacement at a tetrahedral P^{IV} centre can be classified into two major types:

Type 1 : Addition-elimination, involving the formation of a pentacovalent P^{V} intermediate by apical entry of the nucleophile Y, followed by collapse of the intermediate by apical departure of the leaving group X.

Type 2 : Direct displacement ($S_N2(P)$), involving the formation of a pentacoordinate transition state, by synchronous bond-making between phosphorus and Y and bond-breaking between phosphorus and X:



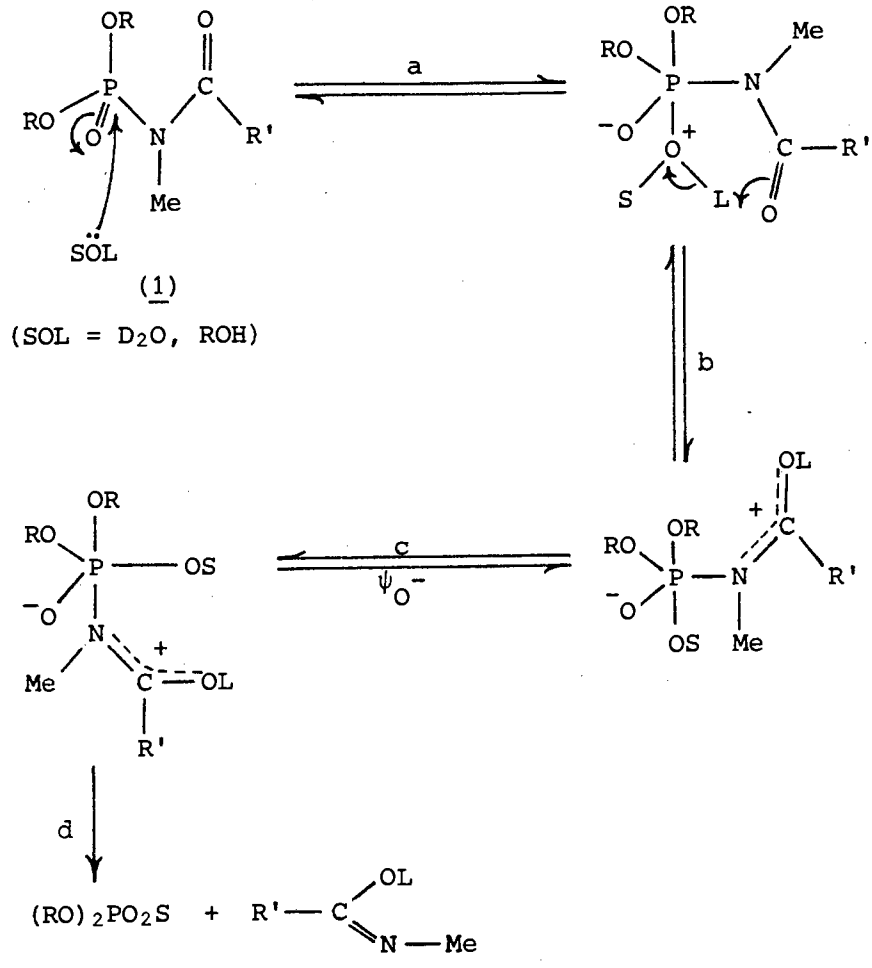
The ease of phosphyl transfer between X and Y is determined by several factors, namely, the nucleophilicity of Y, the steric hindrance, inductive and mesomeric effects of the substituents A and B at phosphorus and the nucleofugality of X. A phosphinyl centre (A, B = alkyl, aryl) is more susceptible to nucleophilic attack than a phosphoryl centre (A, B = O-alkyl, O-aryl), as a result of the relatively low electrophilicity of the latter caused by $p_{\pi} - d_{\pi}$ orbital overlap between the alkoxy/aryloxy substituents and the phosphorus atom. Since the substrates (1c,d,f) all bear the identical

carboxamide leaving group, the operation of a direct displacement $S_N2(P)$ mechanism would imply a considerably faster rate of neutral P(O)-N solvolysis of the phosphinic substrate (1f) than its phosphoric analogues (1c,d); this expectation is in accordance with the observation that $Et_2P(O)Cl$ hydrolyses fifteen times as fast as Et(MeO)P(O)Cl with reaction proceeding via an $S_N2(P)$ mechanism.[50] The reverse reactivity order that is actually observed thus argues against direct displacement solvolysis and indicates the participation of an oxyphosphorane intermediate, the stability and pseudorotational ability of which is governed by the respective ligand apicophilicities.

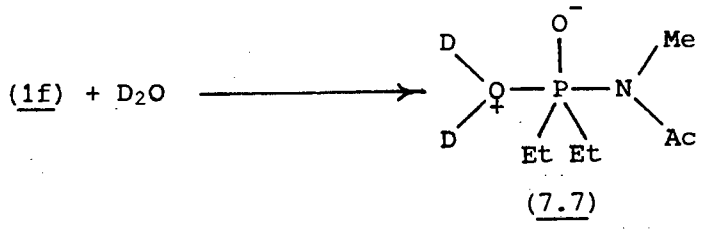
The proposed mechanism of neutral P(O)-N solvolysis of the tertiary substrates (1c,d,e,g) is shown in Scheme 7.2. The relatively high apicophilicity of O-alkyl substituents at phosphorus enables the initial formation of a phosphorane in which the carboxamide group is equatorial. The presence of an additional basic centre in the leaving group (carbonyl oxygen) assists in the required proton transfer to the carboxamide moiety, thus serving to enhance its apicophilicity and promote pseudorotation as illustrated. The protonated carboxamide group departs from an apical position as the tautomeric form of the amide (iminol), effecting P(O)-N cleavage.

The rate-determining step of the P(O)-N solvolysis presumably involves pentacoordinate intermediate formation (pathway a, Scheme 7.2). The observed 2000-fold reactivity difference between the cyclic derivative (1g) and its acyclic analogue (1c) can thus be accounted for in terms of the slow-step rate enhancement typifying the solvolyses of five-membered cyclic phosphates[169] that has been ascribed to the favourable endocyclic O-P-O bond angle reduction (from *ca.* 109° to 90°) caused by the $P^{IV} \rightarrow P^{V}$ transformation.[170]

Scheme 7.2 Proposed mechanism of neutral P(O)-N solvolysis.



The weak apicophilicity of ethyl ligands at phosphorus precludes the P(O)-N solvolysis of (1f) according to the mechanism outlined in Scheme 7.2. The weakly apicophilic ethyl and oxyanion substituents are necessarily anchored in the equatorial position, leaving (7.7) as the only feasible P^{V} intermediate resulting from D_2O attack at (1f):



(7.7)

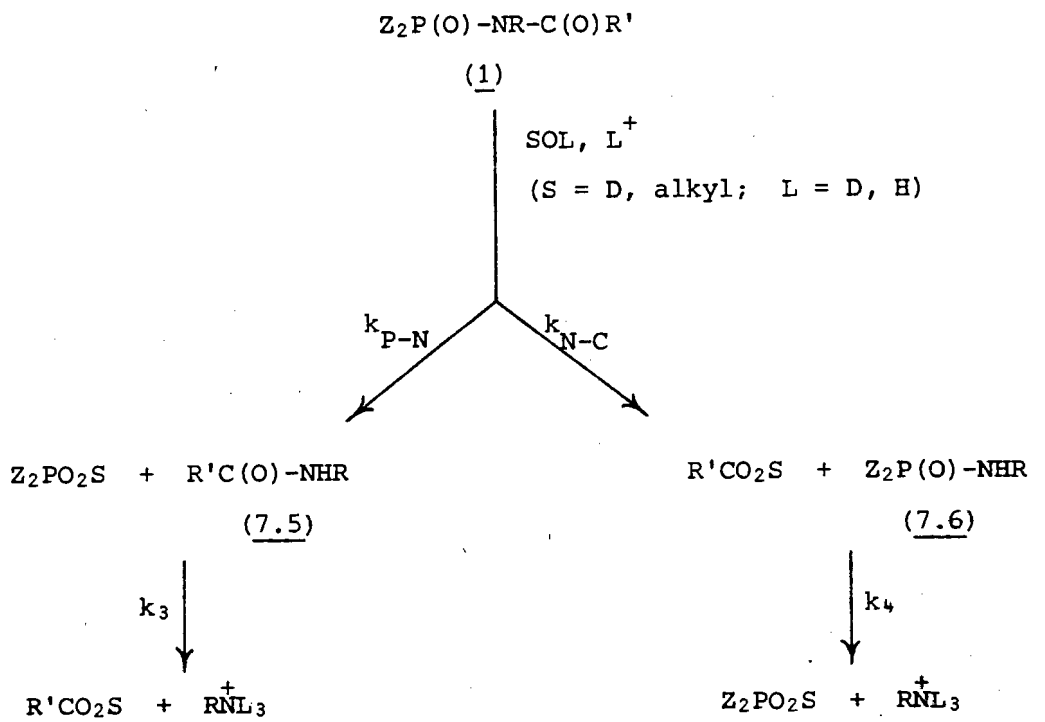
The activation energy for the formation of this intermediate is necessarily high, in view of the disfavoured position of the bulky, weakly apicophilic carboxamide ligand. A reaction temperature significantly higher than 25°C is therefore required in order to effect P(O)-N hydrolysis of (1f).

As discussed above (Chapter 7.1), carboxamides and dialkylphosphylamides are solvolytically stable under neutral conditions. The stability of the N-C(O) linkage in the mixed imide system under neutral conditions thus represents a retention of typical carboxamide solvolytic behaviour. However, the solvolytic instability under neutral conditions of the P(O)-N linkages of all the tertiary N-acyl phosphoramidates contrasts the behaviour of their parent amide systems.[184] The effect of an N-acyl substituent on the dynamics of the P(O)-N bond is two-fold: firstly, it serves to convert the nitrogen-containing function into a relatively poor nucleophile and hence, relatively good leaving group and secondly, competitive predominant resonance interaction of the nitrogen non-bonding electrons with the adjacent carbonyl group results in a decrease in the $p_{\pi} - d_{\pi}$ interaction between nitrogen and phosphorus, thus weakening the P(O)-N bond and significantly increasing the electrophilicity of the phosphoryl centre. These factors, in conjunction with the operation of the mechanism outlined in Scheme 7.2, account for the behaviour of the tertiary phosphoric substrates (1c,d,e,g) as phosphorylating agents under neutral conditions. In this regard, the solvolytic stability of the secondary phosphoric derivatives (1a,b) is more difficult to rationalise;[185] one may suspect ground state stabilisation of the secondary substrates in the hydroxylic solvents, by solvation involving extensive hydrogen bonding.

7.3 ACID-CATALYSED SOLVOLYSIS

Although the solvolysis of a mixed imide can proceed via the same pathways in both neutral and acidic media, the acidic solvolysis scheme is complicated by the instability of the amide products (7.5) and (7.6), which may undergo subsequent N-acyl cleavage, as illustrated in Scheme 7.3.

Scheme 7.3 Acid-catalysed solvolysis of the mixed imides.



7.3.1 ACID-CATALYSED ALCOHOLYSIS

The rates and orientation of the reaction of (1c) in acidic methanol and ethanol were determined by GC (Chapter 9.5.1). All reactions were found to follow pseudo first order kinetics and the appropriate rate constants (k_{P-N}, k_{N-C}) were evaluated by following the variations in substrate and product concentrations as a function of time. The products of initial P(O)-N cleavage are relatively unreactive in the acidic alcohol solutions ($t_{\frac{1}{2}}$ > 2 months), whereas the phosphoramide produced by N-C(O) alcoholysis

of (1c) is relatively unstable and subsequently cleaves to the same phosphoric ester as that produced by P(O)-N cleavage of the mixed imide, at an independently determinable rate.[186] The rate constants were determined by monitoring both the appearance of N-methylacetamide (k_{P-N}) and the disappearance of the mixed imide ($k_{P-N} + k_{N-C}$). The results thus obtained are summarised in Table 7.3a. A comparison of the neutral and acid-catalysed alcoholysis rates of substrate (1c) provides a preliminary indication of the response of the P(O)-N and N-C(O) solvolyses to the acidity of the medium, as indicated in Table 7.3b.

Table 7.3a The acid-catalysed alcoholysis of (1c) (25°C).

Medium	P-N cleav. %	N-C cleav. %	$10^5 k_{\psi(P-N)}$ s^{-1}	$10^5 k_{\psi(N-C)}$ s^{-1}
0.86 M HCl in MeOH	91.9	8.1	4.0	43.5
0.86 M HCl in EtOH	80.8	19.2	0.95	3.8

Table 7.3b Medium acidity response of the P(O)-N and N-C(O) alcoholyses of (1c) (25°C).

Medium change	Rate acceleration P-N	N-C
Neutral MeOH → 0.86 M HCl/MeOH	20	>4400[a]
Neutral EtOH → 0.86 M HCl/EtOH	6	> 480[a]

[a] Since exclusive P(O)-N cleavage is observed in neutral alcohol ($k_{\psi(N-C)} < 0.05\ k_{\psi(P-N)}$), this value represents the lower limit of the rate acceleration.

The significantly greater labilising influence of acid on the N-C(O) than P(O)-N linkage of the mixed imide, completely contrasts the acidity response shown by the parent amide systems. The lack of susceptibility of the P(O)-N alcoholysis of (1c) to acid catalysis is reminiscent of the resistance to acid catalysis displayed by related N-acyl phosphoramidic acid derivatives (acyl = carboxyacyl, sulfonyl, phosphoryl).[24] These observations support the view that N-protonation, rather than O-protonation, is responsible for the characteristically facile acidic solvolysis of phosphylamides, since N-acylation effectively eliminates the nitrogen atom as a competitive basic centre. Similarly, the remarkable sensitivity of the N-C(O) alcoholysis rate of (1c) to the acidity of the medium is atypical of the behaviour of the relatively unreactive parent carboxamide system. The dynamics of the phosphoryl-nitrogen and nitrogen-carbonyl bonds are therefore apparently substantially modified in the mixed imide system.

7.3.2 ACID-CATALYSED HYDROLYSIS

A systematic study of the rate-acidity dependence of the P(O)-N and N-C(O) hydrolyses of substrates (1d) and (1f) and selected related mono- and diacylamines was conducted with the aim of firstly, quantifying the acyl substituent effects upon the dynamics of the phosphyl-nitrogen and nitrogen-carbonyl bonds and secondly, utilising the rate-water activity dependence to provide mechanistic information.

The rates and orientation of the reaction of (1d) and (1f) in D_2O - D_2SO_4 mixtures were determined by ^1H NMR spectroscopy. Measurement of the hydrolysis rates by monitoring the variation of substrate and product concentrations with time, requires a knowledge of the behaviour of the amide products (7.5a) and (7.6a,b) in the same acidic media.

$MeC(O)-NDMe$	$(EtO)_2P(O)-NDMe$	$Et_2P(O)-NDMe$
(7.5a)	(7.6a)	(7.6b)

Besides serving this function, the independent determination of the hydrolytic behaviour of the parent amides provides reference kinetic data for comparative purposes. In addition, the response of the P(O)-N and C(O)-N hydrolyses of the phosphoric and carboxylic imides (7.8) and (7.9a,b) to medium acidity, was investigated in order to compare the hydrolytic behaviour of the mixed diacylamines with their symmetrical counterparts.

$[(EtO)_2PO]_2NMe$	$(MeCO)_2NMe$	$MeC(O)-NMe-COPh$
(7.8)	(7.9a)	(7.9b)

RESULTS AND DISCUSSION

1. Kinetics

All reactions were conducted at 25°C and were monitored by ^1H NMR spectroscopy. The hydrolyses were found to follow pseudo first order kinetics (eq. 7.6). The highly reactive nature of the reference phosphylamides (7.6a,b) over the entire acid range precludes the measurement of their rates of hydrolysis at 25°C, by means of the NMR technique and as such, a lower limit rate constant can, at best, be estimated (Scheme 7.3, $k_4 > 5 \times 10^{-3}$ s^{-1}). In contrast, the reference carboxamide (7.5a) is remarkably resistant to acid-catalysed hydrolysis over the acid range of interest (Scheme 7.3, $k_3 << k_{P-N}, k_{N-C}$). The hydrolytic behaviour of the amide products (7.5) and (7.6) thus enabled determination of the orientation and rates of hydrolysis of (1d,f) by monitoring the appearance of (7.5a) (k_{P-N}), acetic acid (k_{N-C}, 1d) or methylammonium ion (k_{N-C}, 1f) and the disappearance of the substrate ($k_{P-N} + k_{N-C}$). The ^1H NMR signals selected to monitor the substrate disappearance and product appearance during the hydrolysis of (7.5a), (7.9a),

Table 7.4 Solvolysis of (1d) in D_2O - D_2SO_4 mixtures (25 ± 0.5°C).

D_2SO_4 % wt.	P-N cleav. %	N-C cleav. %	$10^5 k_{\psi(P-N)}$ s^{-1}	$10^5 k_{\psi(N-C)}$ s^{-1}
0.8		100		0.40
1.6		100		0.85
3.3		100		1.55
8.0		100		4.47
15.5		100		10.0
20.0		100		13.8
22.6		100		15.8
29.2		100		19.9
40.0		100		27.5
45.0		100		30.0
52.4	15.1	84.9	5.37	30.2
62.3	63.4	36.6	33.1	19.1
71.3	81.1	18.9	45.7	10.7
79.4	68.6	31.4	38.5	17.6
86.9	44.5	55.5	25.7	32.0

Table 7.5 Solvolysis of (1f) in D_2O - D_2SO_4 mixtures (25 ± 0.5°C).

D_2SO_4 wt. %	P-N cleav. %	N-C cleav. %	$10^5 k_{\psi(P-N)}$ s^{-1}	$10^5 k_{\psi(N-C)}$ s^{-1}
1.6	70.9	29.1	0.25	0.10
3.3	67.5	32.5	0.47	0.23
6.4	70.5	29.5	1.09	0.46
16.1	75.6	24.4	4.68	1.51
20.0	73.8	26.2	5.13	1.82
22.6	73.8	26.2	5.75	2.04
29.2	78.3	21.7	10.6	2.96
40.3	86.3	13.7	24.0	3.80
52.4	100		52.6	
62.3	100		121[a]	
79.4	100		104[c]	
83.2	100		116[a]	

[a] ± 20%

Table 7.6 Solvolysis of (7.5a) and (7.9a) in D_2O - D_2SO_4 mixtures (25 ± 1°C).

D_2SO_4 wt. %	(7.5a) $10^8\ k_{\psi(N-C)}$ s^{-1}	(7.9a) $10^4\ k_{\psi(N-C)}$ [a] s^{-1}
0.8		0.81
1.6	5.56	1.17
3.3	11.2	2.75
8.0	22.6	6.03
15.5	24.2	9.21
22.6	20.9	18[b]
29.2	15.4	21[b]
40.0	8.33	[c]
45.0	6.46	[c]
52.4	4.41	[c]
62.3	2.79	[c]
79.4	1.63	[c]
83.2	[d]	18[b]
86.9	[d]	19[b]
98.0	[d]	3.54

[a] $k_{\psi(N-C)} = 0.5\ k_{\psi}^{obs.}$; [b] ± 20%

[c] $k > 5 \times 10^{-3}\ s^{-1}$; [d] $k < 1 \times 10^{-8}\ s^{-1}$

(1d) and (1f) are illustrated in Figs. 7.2a-d respectively.

The rate-acidity data are summarised in Tables 7.4 - 7.6. The logarithmic rate profiles, as a function of acidity, are shown in Fig. 7.3. The shape of the rate profile of (7.5a) with a maximum occurring at *ca.* 14% D_2SO_4 is typical of an A2 carboxamide hydrolysis mechanism. The existence of a rate maximum is a consequence of the two opposing effects of increasing medium acidity on the rate of a bimolecular acid-catalysed hydrolysis reaction, namely, increasing equilibrium concentration of the reactive conjugate acid form of the substrate, with concomitant reduction in the availability of water. In contrast, the N-C(O) hydrolysis rate of (1d) attains a maximum at a significantly higher acidity (52% D_2SO_4) and as such, is more reminiscent of the rate-acidity profiles associated with the acid-catalysed hydrolysis of carboxylic esters[187] rather than amides.[171] Owing to predominant P(O)-N cleavage at higher acidity, the rate of N-C(O) cleavage of (1f) is only determinable up to 40% D_2SO_4. In addition, the measurement of a complete rate-acidity profile of the carboxylic imide (7.9a) is precluded by its hydrolytic instability in the range of 25 to 80% D_2SO_4. However, despite their incomplete rate-acidity profiles, the monotonic increase in N-C(O) hydrolysis rates of both (1f) and (7.9a) within the observable low acidity range, indicates the occurrence of their rate maxima at comparatively high acidity, as observed for (1d).

The rate of P(O)-N hydrolysis of (1d) cannot be measured over the 1 - 52% D_2SO_4 range, owing to the predominance of competitive N-C(O) cleavage ($k_{P-N} < 0.05\ k_{N-C}$). However, P(O)-N cleavage becomes increasingly detectable at higher acidities and its hydrolysis rate is found to rapidly increase to a maximum at 70% D_2SO_4, whereafter a steady decrease in rate is observed. The rates of P(O)-N and N-C(O) hydrolyses of (1f) are comparable up to 40% D_2SO_4, but at higher acidities, exclusive P(O)-N cleavage is observed, with maximisat-

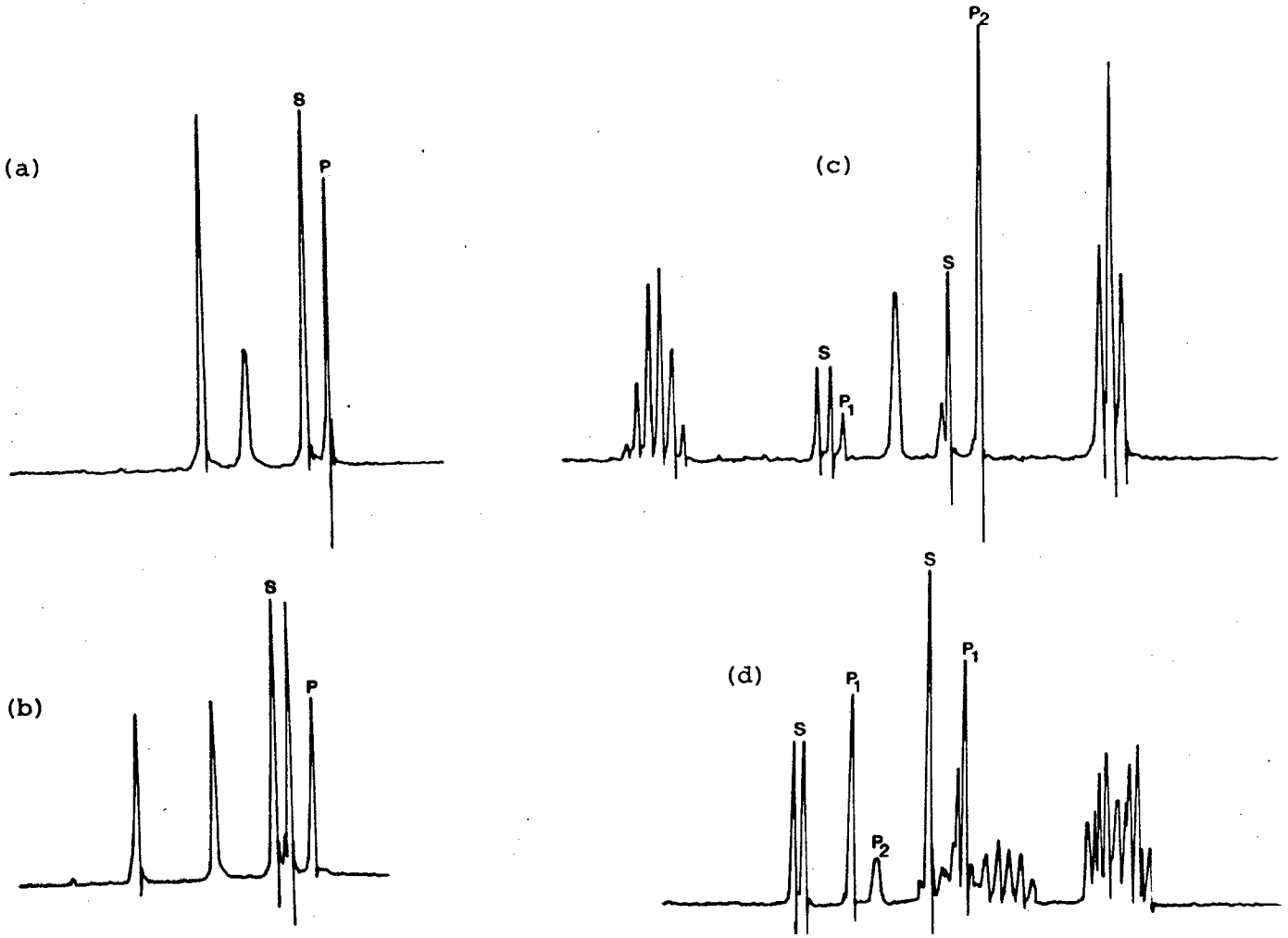


Figure 7.2 ^{1}H NMR signals selected to monitor the substrate (S) disappearance and product (P) appearance in D_2O-D_2SO_4 mixtures at 25°C: (a) S = (7.5a); P = $MeCO_2D$; (b) S = (7.9a); P = MeCONDMe; (c) S = (1d); P1 (P-N cleavage product) = MeCONDMe; P2 (N-C cleavage product) = $MeCO_2D$; (d) S = (1f); P1 (P-N cleavage product) = MeCONDMe; P2 (N-C cleavage product) = $Me\overset{+}{N}D_3$.

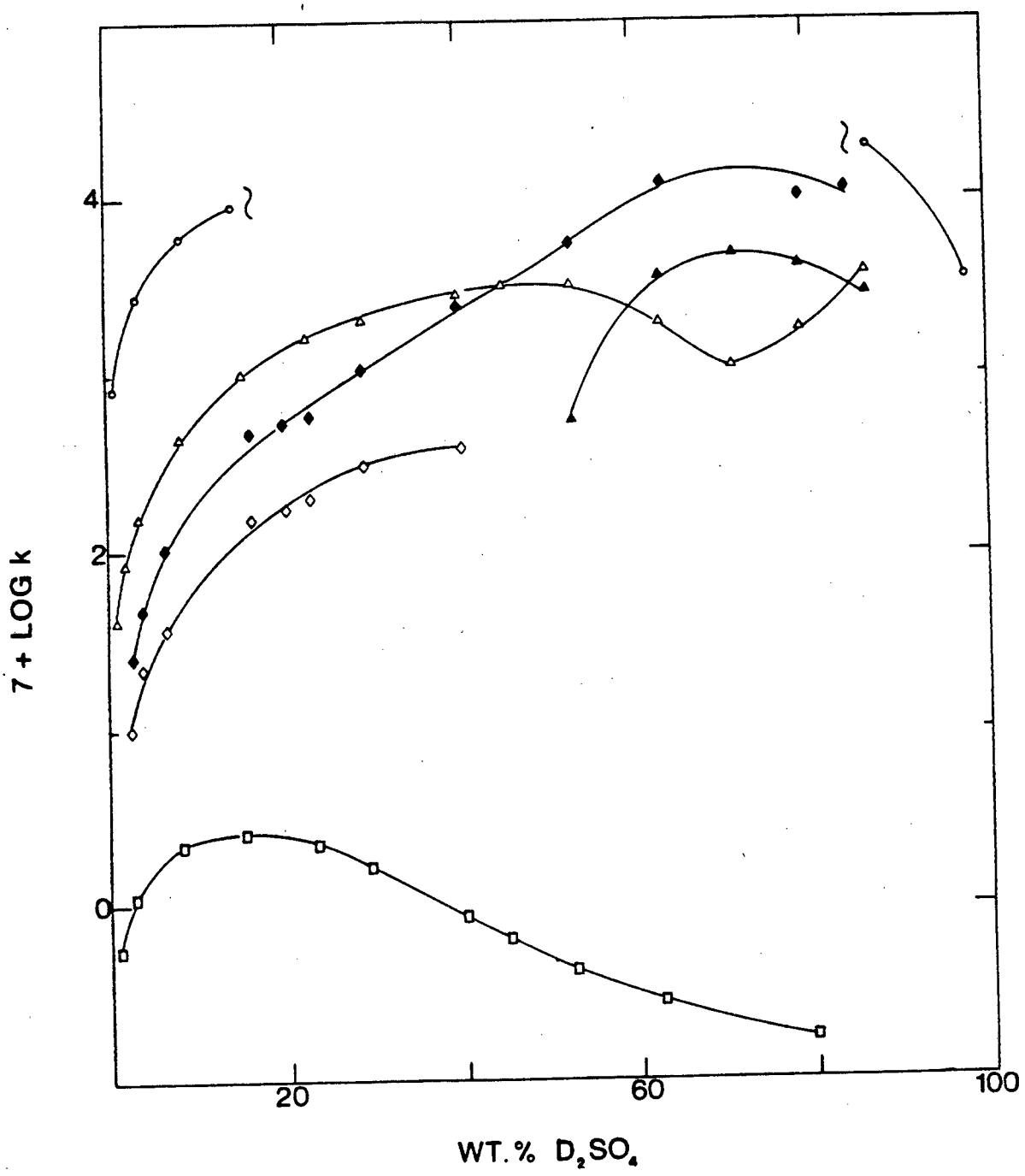


Figure 7.3 Rate-acidity profiles: (7.5a), — □ — ; (1f), N-C cleavage, — ◇ — ; (1f), P-N cleavage, — ◆ — ; (1d), N-C cleavage, — △ — ; (1d), P-N cleavage, — ▲ — ; (7.9a), — o — .

ion occurring at approximately the same acidity as that required for maximal P(O)-N hydrolysis of (1d) (70% D_2SO_4).

The phosphoric imide (7.8) is indefinitely stable at 25°C in the entire range of D_2O - D_2SO_4 mixtures and its rate-acidity profile is thus not shown in Fig. 7.3. The various classes of compounds discussed above can thus be ordered with respect to reactivity in aqueous acidic media, as follows:

P(O)∮N : Phosphoric imides << Mixed imides < Phosphoric amides

N∮C(O) : Carboxylic amides < Mixed imides < Carboxylic imides

Quantitative comparisons of the reactivities of these systems are given in Tables 7.7 and 7.8. The introduction of an acyl (MeCO or Z_2PO; Z = EtO, Et) substituent at nitrogen has opposite effects upon the dynamics of the P(O)-N and N-C(O) bonds: it dramatically stabilises the former, whereas it significantly labilises the latter towards acid-catalysed solvolysis.

Table 7.7 Relative rates of bond cleavage of X-NMe-COMe and Z_2PO-NMe-Y in 30% D_2SO_4 at 25°C.

Substrate	X	Y	Z	Relative Rate P(O)-N	Relative Rate N-C(O)
(1d)	$(EtO)_2PO$	COMe	EtO	<70[a]	1450
(1f)	Et_2PO	COMe	Et	740	200
(7.5a)	D	-	-	-	1
(7.6a)	-	D	EtO	>35000[b]	-
(7.9a)	MeCO	-	-	-	15900
(7.8)	-	$PO(OEt)_2$	EtO	<1[c]	-

[a] $k_{\psi(P-N)} < 0.05\ k_{\psi(N-C)}$; [b] $k > 5 \times 10^{-3}\ s^{-1}$; [c] $k < 1 \times 10^{-8}\ s^{-1}$.

Table 7.8 Relative rates of N-C(O)Me cleavage of X-NMe-COMe in 15.5% D_2SO_4 at 25°C.

Substrate	(7.5a)	(1f)	(1d)	(7.9b)	(7.9a)
X	D	Et_2PO	$(EtO)_2PO$	PhCO	MeCO
Rel. rate	1	23	410	1580	3780

The acid-catalysed hydrolysis of a weakly basic substrate B, such as an amide, involves a rapid pre-equilibrium protonation of the substrate, followed by rate-determining nucleophilic attack on the conjugate acid. The overall reaction can be represented by eq. 7.7:

$$B + H^+ \underset{\text{fast}}{\overset{K_{BH^+}}{\rightleftharpoons}} BH^+$$

$$BH^+ + rH_2O \xrightarrow[\text{slow}]{k} B^{\ddagger} \longrightarrow \text{products} \qquad [7.7]$$

The pseudo first order rate constant can be expressed in terms of the rate constant of the slow step (k) and the dissociation constant of the substrate conjugate acid (eq. 7.8):

$$k_\psi = \frac{k \quad f_B}{K_{BH^+} \quad f_{B^{\ddagger}}} \cdot a_{H^+} \qquad [7.8]$$

If one assumes that the activity coefficient ratios ($f_B/f_{B^{\ddagger}}$) for a pair of structurally related substrates are approximately the same, then the ratio of the rate-determining steps of their hydrolyses in the same acidic medium can be estimated from eq. 7.9:

$$\Delta \log k \cong \Delta \log k_\psi - \Delta pK_{BH^+} \qquad [7.9]$$

The interpretation of the kinetics of reactions involving substrate activation by preprotonation therefore requires a knowledge of the extent of protonation

of the reactants in a given acidic medium and, in systems involving more than one basic centre (e.g. amides, imides), a knowledge of the protonation site assists in formulating the reaction mechanism.

2. Ionisation Behaviour

Provided the specific acidity function, H_B, obeyed by the weakly basic substrate B is known, the basicity constant K_{BH^+} can be determined by measurement of the ionisation ratio I ($[BH^+]/[B]$) of the substrate in a series of acidic solutions and application of eq. 7.10:

$$\log I = -H_B + pK_{BH^+} \qquad [7.10]$$

If the pK_{BH^+} value is to have any thermodynamic significance, the acidity function chosen must satisfy two requirements: (i) the slope of the plot of log I vs. H_B should be minus unity (eq. 7.10); (ii) a similarity in the activity coefficient behaviour of the base and its conjugate acid and that of the indicator base-conjugate acid pairs used in defining the particular acidity function, is required. The first condition is necessary and, in most cases, sufficient.

Ideally, each individual base requires its own acidity function. However, owing to the obvious difficulties involved in determining such a unique function, one commonly selects an acidity function defined by closely related indicator bases, provided one exists. In cases where the above conditions are not met, several empirical approaches may be employed: that of Yates[187] recognises that acidity functions are linearly related to one another and utilises eq. 7.11, where H_X is an established acidity function (e.g. H_o, H_A) and c and m are constants:

$$\log I = -mH_X + c \qquad [7.11]$$

The generally accepted quantification of basicity from non-unit slope plots of eq. 7.11 is the value of the acidity function at half-protonation ($pK_{BH^+} = H_{X^{\frac{1}{2}}} = c/m$); however, this value does not correspond to the thermodynamic pK_{BH^+}.[188] This approach has been used in estimating the basicities of aliphatic amides,[189a] carbamates,[189b] aromatic amides and phenylureas[189c] from log I vs. $-H_A$ plots and of phosphine oxides and sulfides[94] from plots of log I vs. $-H_o$. Alternatively, other workers consider the intercept c, as the best pK_{BH^+} estimate ($pK_{BH^+} = mH_{X^{\frac{1}{2}}} = c$), as illustrated by the reported basicity constants of acetanilides[190a] ($H_X = H_A$), ketones[190b] and aliphatic esters[190c] ($H_X = H_o$). For substrates yielding m values outside the range 0.9 - 1.1, the difference between the two estimates (c and c/m) becomes considerable and must be taken into account in comparative studies.

Common to the above method (eq. 7.11) and to the alternative Bunnett-Olsen[191] and X-function[192] methods for determining basicity constants, is the necessity for ionisation ratio measurement, which in turn, relies upon the change in some observable (typically spectroscopic) property of the base, upon protonation. The protonation of aromatic bases can be followed by monitoring UV spectral changes, whereas NMR and Raman spectral shifts are applicable to the protonation study of aliphatic bases. Owing to their weak UV absorption,[193] the NMR method is more appropriate for investigating amide protonation, in which ionisation ratios are calculated from eq. 7.12 (Chapter 9.5.2):[194]

$$I = (\Delta\nu - \Delta\nu_B)/(\Delta\nu_{BH^+} - \Delta\nu) \qquad [7.12]$$

The ^1H NMR acetyl singlets of (1d) and (7.5a) were used as the probe signals for ionisation measurements. Ionisation data could not be obtained for substrates (7.6a,b) and (7.9a,b), owing to their instability in aqueous acidic media. The sigmoidal dependence of $\Delta\nu$ upon the acidity function of the

medium is illustrated in Fig. 7.4, where D_A corresponds to the amide acidity function of D_2O - D_2SO_4 mixtures. The relationship between H_A and D_A is discussed in Chapter 9.5.2. Although the plots of eq. 7.11 ($H_X = D_A$) for the ionisation of (1d) and (7.5a) are linear within the range $-1 \leq \log I \leq 1$ (Fig. 7.5), the slopes m differ from the ideal value of unity.[188] The slopes, intercepts (c) and $D_{A\frac{1}{2}}$ values of substrates (1d) and (7.5a) are listed in Table 7.8.

Table 7.8 Ionisation behaviour in D_2O - D_2SO_4 mixtures (25°C).

Substrate	m	c	$D_{A\frac{1}{2}}$	Acidity (%) at half-protonation
(1d)	0.95	-3.31	-3.49	69.4
(7.5a)	1.25	-0.60	-0.48	9.6

The ionisation behaviour of (7.5a) in H_2O - H_2SO_4 mixtures has been previously investigated by ^1H NMR spectroscopy;[189a] the reported $H_{A\frac{1}{2}}$ value of -0.70 (m = 1.08) is 0.2 acidity function units lower than the $D_{A\frac{1}{2}}$ value quoted in Table 7.8. Since the acid strength of BH^+ in H_2O is greater than that of BD^+ in D_2O, it follows that $pK_{BH^+} < pK_{BD^+}$, thus accounting for the observed discrepancy.[195]

There is a paucity of information concerning the ionisation behaviour of diacylamine systems. N-Acetyl thiourea, $H_2NC(S)-NH-C(O)Me$ (7.10), undergoes thiocarbonyl protonation following H_o''' in 35 - 60% H_2SO_4 ($pK_{BH^+} = -4.64$) and carbonyl oxygen protonation following H_A in 65 - 96% H_2SO_4 ($pK_{BH_2{}^{2+}} = -4.61$).[198] The protonation of a variety of carboxylic imides in superacidic media, has been qualitatively investigated and found to involve both mono- and diprotonation at carbonyl oxygen, depending upon the acid:imide ratio:[199]

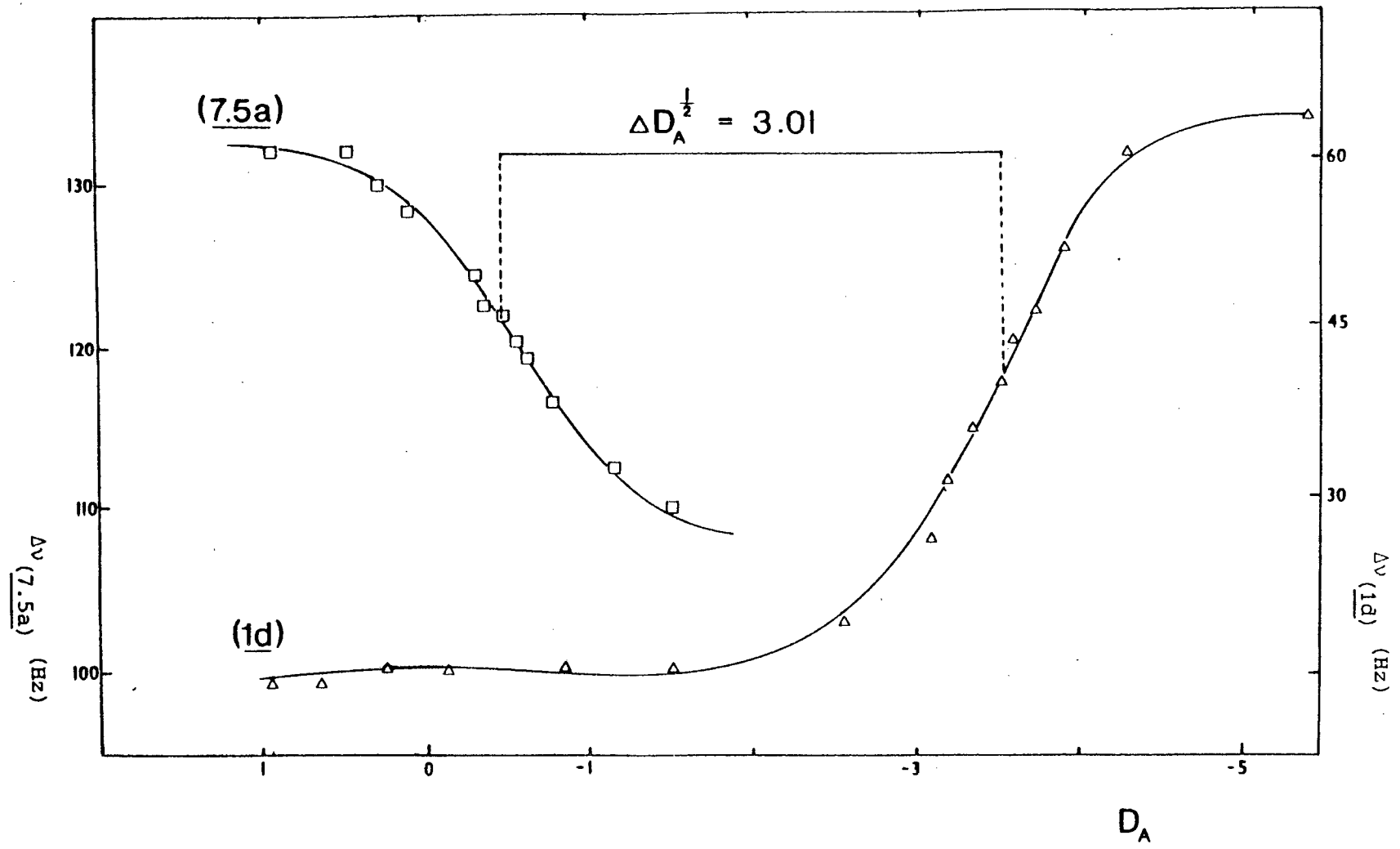


Figure 7.4 Protonation-induced shifts (at 100 MHz) of the acetyl methyl chemical shifts of (1d) (— △ —) and (7.5a) (— □ —) as a function of the medium acidity.

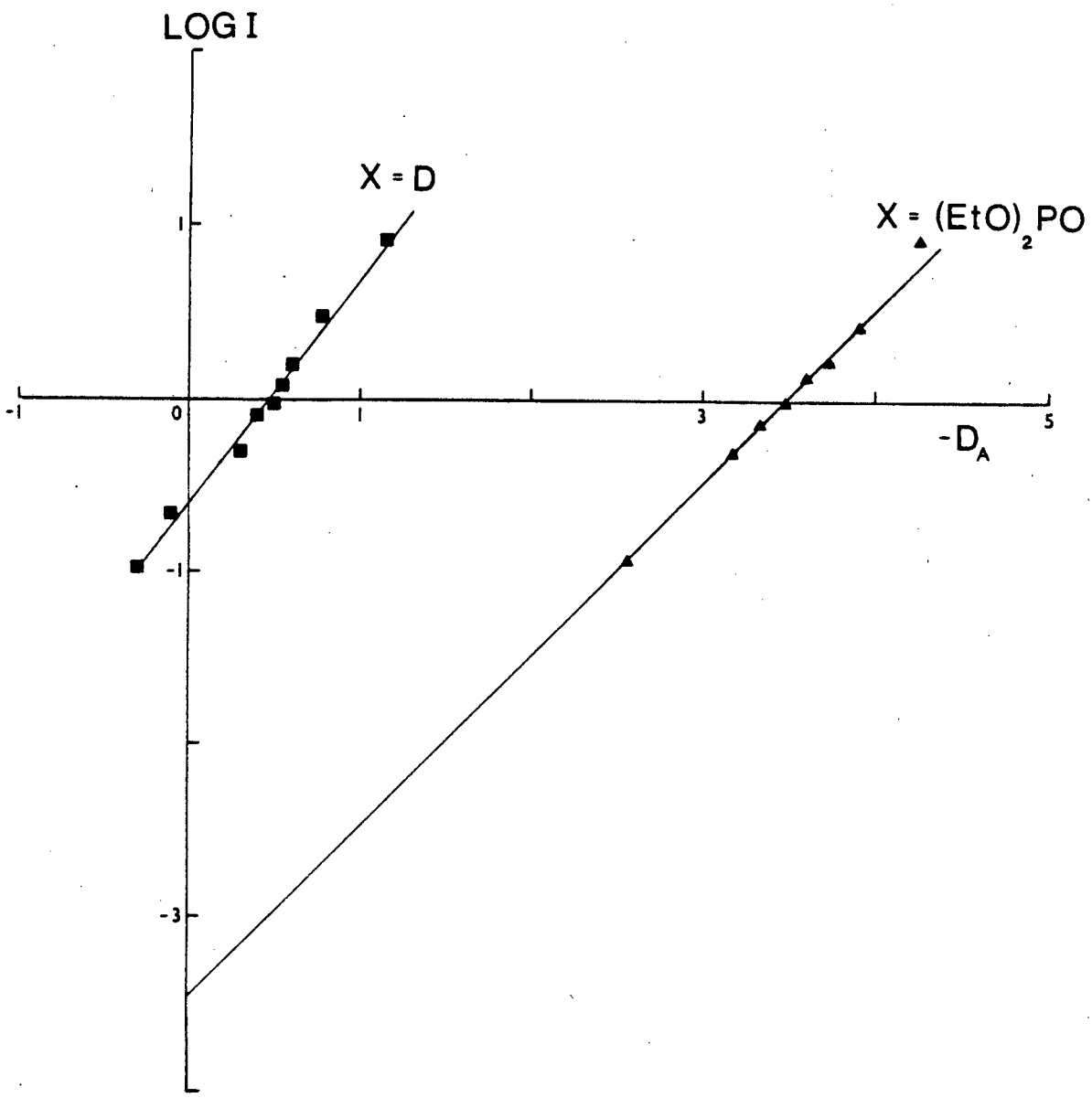
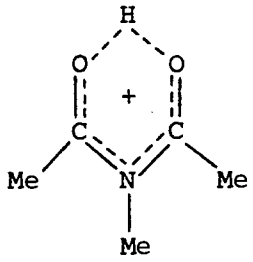
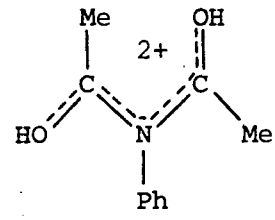


Figure 7.5 The ionisation behaviour of X-NMe-COMe.



(7.11)

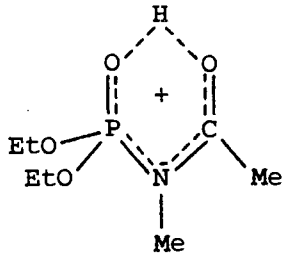
Ratio: 1.5 : 1



(7.12)

10 : 1

The observation that the mixed imide (1d) follows the amide acidity function D_A (m = 0.95),[200] is indicative of protonation of the carboxamide moiety. Since the favoured protonation site of carboxylic amides is the carbonyl oxygen, it appears that the acetyl methyl chemical shift change of (1d), observed in the 50 - 85% D_2SO_4 range, occurs in response to carbonyl oxygen protonation of the mixed imide. The conjugate acid may be internally stabilised by the phosphoryl group to yield the cyclic structure (7.13), particularly in view of the fact that monoprotonated carboxylic imides (e.g. (7.11)), anhydrides and β-diketones have been proposed to exist in analogous cyclic forms.[199a]



(7.13)

A comparison of the protonation-induced downfield shifts of the acetyl and N-methyl absorptions of substrates (1d) and (7.5a) is given in Table 7.9.

Table 7.9 Chemical shifts (Hz) caused by protonation.[a]

Substrate	$\Delta\Delta\nu_{Ac}$	$\Delta\Delta\nu_{NMe}$	$\Delta\Delta\nu_{Ac}/\Delta\Delta\nu_{NMe}$
(1d)	35.0	17.5	2.0
(7.5a)	34.2	23.5	1.5

[a] Spectra recorded at 100 MHz.

The relatively small N-methyl shift of (1d) compared to that of the parent carboxamide (17.5 and 23.5 Hz respectively), supports the proposal of phosphoryl group participation in the delocalisation of positive charge within the carbonyl oxygen protonated form of the mixed imide conjugate acid (structure (7.13)). It is of interest to note that the N-methyl absorption of the symmetrical phosphoric imide (7.8) undergoes an extremely small protonation-induced shift ($\Delta\Delta\nu$ = 4.5 Hz) in the 50 - 90% D_2SO_4 range. In view of the stability of the P(O)-N linkage of (7.8) in the aqueous acidic media (at 25°C), the likely site of protonation of this substrate is at phosphoryl oxygen, rather than nitrogen. The small shift within the acid range studied is thus indicative of either incomplete protonation, or a weak response of the N-methyl chemical shift to the development of positive charge at the phosphorus atom. If one assumes similar phosphoryl oxygen basicities of (1d) and (7.8), it is clear that the 17.5 Hz downfield shift of the N-methyl proton absorption of the former within the 50 - 85% D_2SO_4 range can only be explained in terms of carbonyl oxygen protonation.

The N-diethylphosphorylation of N-methylacetamide thus results in a one-thousand-fold decrease in basicity ($\Delta pK_{BH^+} \cong -3$) without affecting the site of protonation, namely, the carbonyl oxygen. Although the pK_{BH^+} values of imides (7.9a,b) could not be determined, the N-acetylation or benzoylation

of the same carboxamide would undoubtedly lead to an even more pronounced basicity reduction. On the other hand, the N-acylation (acyl = acetyl, phosphoryl) of the phosphoramide (7.6a) reduces the nitrogen atom basicity to such an extent as to preclude the formation of the kinetically important form of the substrate conjugate acid. A knowledge of the modification in ionisation behaviour, brought about by structural variation at the nitrogen atom, assists in mechanistic elucidation.

3. Acidic Solvolysis Mechanisms

The variation in concentration of the reacting species, water, that can be achieved in concentrated acidic solution, enables important mechanistic information to be deduced from kinetic investigations conducted therein. However, the theoretical interpretation of the rate-acidity dependence is fraught with difficulties that arise, in part, from the use of acidity functions in the quantification of medium acidity. Historically, the first quantitative approach towards the treatment of rate-acidity dependence in non-dilute solution, was made by Zucker and Hammett[201a] who sought to categorise reactions into either the unimolecular (A1), or bimolecular (A2) types of rate-determining conversion of the protonated substrate to the transition state. This approach was followed by Bunnett's[201b] attempt to classify acid-catalysed reactions according to the number of water molecules taking part in the transition state. The Modified Hydration Parameter Treatment developed by Yates and co-workers[188,202] minimised the seriousness of the approximations involved in Bunnett's approach,[191] thus allowing for a more simple mechanistic interpretation of the rate-water activity dependence. Moodie *et al.*[203] developed a more direct hydration treatment, involving neither an acidity function nor a basicity constant term, but requiring a knowledge of the ionisation ratio of the substrate in a given acidic solution;

this approach has been extensively applied to the elucidation of hydrolysis mechanisms.[181,182] The most recent and satisfactory approach to this problem is the Transition State Activity Coefficient (TSAC) approach developed by Yates and Modro,[204] which utilises the acidity dependence of the transition state activity coefficient as a mechanistic criterion.

a. Phosphyl-Nitrogen Cleavage

The Zucker-Hammett approach, which categorises acid-catalysed reaction mechanisms as A1 or A2, depending upon whether log k_ψ is linear, with approximately unit slope, in $-H_o$ or log c_{H^+}, was applied to the phosphinyl-nitrogen hydrolysis of substrate (1f). A linear relationship of slope 0.4, exists between log k_ψ and $-D_o$, in contrast to the clearly non-linear dependence of log k_ψ on log c_{D^+}. As illustrated in Fig. 7.6, log k_ψ is linearly dependent upon $-D_A$ with a slope of 0.80, indicating that the amide acidity function (D_A) describes the protonation of (1f) better than does D_o. The clearly non-linear dependence of log k_ψ on log c_{D^+} (Fig. 7.6) argues against a bimolecular P(O)-N hydrolysis mechanism. Haake *et al.*[205] have reported analogous positive curvature in the Zucker-Hammett plot for the hydrolysis of N-p-nitrophenyl diphenylphosphinamide and, in view of the unit slope linear dependence of log k_ψ on $-H_A$, have proposed an A1 mechanism for the P(O)-N hydrolysis of this substrate. The observed kinetic solvent isotope effect (k_H/k_D = 0.37) is consistent with advanced departure of the poor nucleophile, p-nitroaniline, in the rate-determining transition state.

Both p-nitroaniline and N-methylacetamide are relatively weak bases (pK_a values 1.0[206] and -0.7[189a] respectively) and hence, poor nucleophiles. Therefore, in accordance with the argument of Haake *et al.*[205] the P(O)-N hydrolysis of (1f) should have even greater A1 character than that of the phosphinanilide. This mechanistic conclusion is supported by the linear

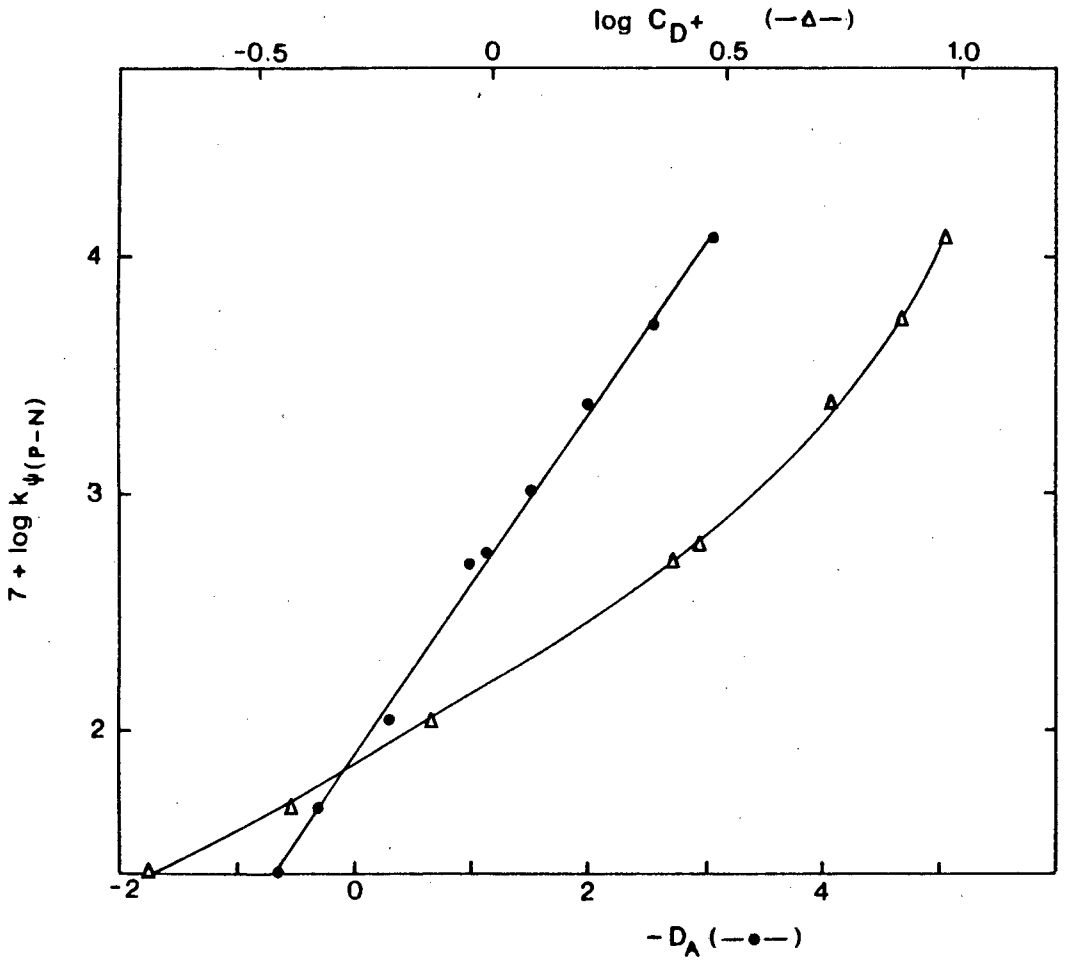
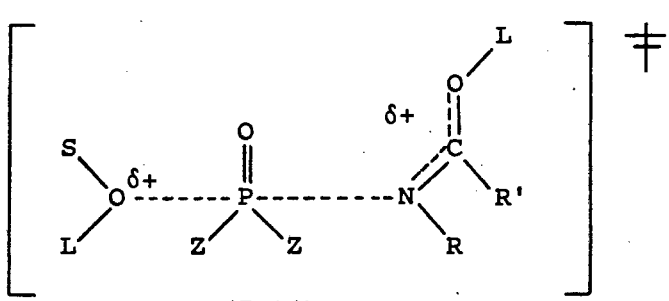


Figure 7.6 The Zucker-Hammett plots for the P(O)-N hydrolysis of (1f) in D_2O-D_2SO_4 mixtures at 25°C.

dependence (albeit non-unit slope) of log k_ψ on $-D_A$, illustrated in Fig. 7.6. However, owing to the activity coefficient ratio assumptions inherent in the Zucker-Hammett Hypothesis, its use as a serious mechanistic criterion is questionable and conclusions derived from its application must be treated with due caution.

The rate of a unimolecular acid-catalysed hydrolysis reaction increases monotonically with acidity, by virtue of its insensitivity to decreasing water availability. However, the rate-acidity profile for P(O)-N hydrolysis of (1f) (Fig. 7.3) shows a poorly defined rate maximum at *ca.* 70% D_2SO_4, implying a certain dependence upon water activity and thus, argues against a pure A1 mechanism. The existence of a spectrum of mechanisms ranging from the associative A2 to the dissociative A1 has been proposed[205] in an attempt to describe mechanisms having characteristics of both extreme types. The extent of P(O)-N bond cleavage in the transition state determines the position of such a "merged A1 - A2" mechanism along the A1 - A2 continuum.

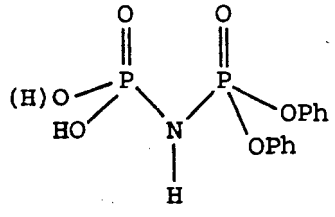
As observed for substrate (1d), the likely protonation site of (1f) is at the carbonyl oxygen, enabling advanced departure of the tautomeric form of N-methylacetamide in the rate-determining transition state. The incipient phosphinilium ion is stabilised by an incoming water molecule that prevents the unfavourable development of positive charge at the phosphorus atom. The acid-catalysed displacement of a carboxamide from a mixed imide thus proceeds via a direct displacement $S_N2(P)$ mechanism with extensive departure of the leaving group evident in the rate-determining transition state (7.14):



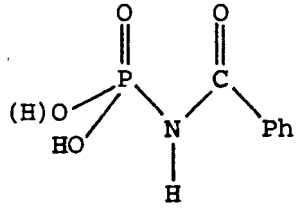
(7.14)

The overall rate of acid-catalysed P(O)-N solvolysis is thus expected to depend upon the nucleophilicity of the solvent, the electrophilicity of the phosphyl centre (as determined by the electronic and steric nature of substituents Z), as well as the basicity of the carboxamide residue and the nucleofugality of its iminol form.

The P(O)-N linkage of the symmetrical diacylamine (7.8) shows a greater resistance to acid-catalysed solvolysis than the P(O)-N linkage of the unsymmetrical diacylamine system (1). This observation is in agreement with that of Halmann *et al.*[24] concerning the comparative hydrolytic reactivities of the phosphoramides (7.15) and (7.16): at pH 4, the rate difference of the corresponding monoanions is thirty-fold, in favour of the N-benzoyl derivative (7.16) and whilst the P(O)-N hydrolysis of (7.16) responds to acid catalysis in strongly acidic media, that of the N-diphenylphosphoryl derivative (7.15) remains completely insensitive to the acidity of the medium.



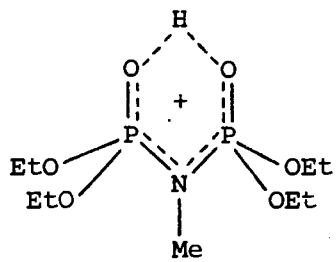
(7.15)



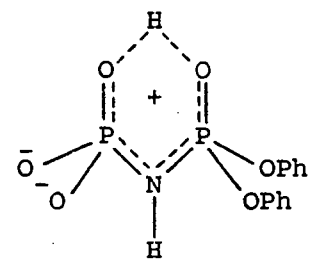
(7.16)

The greater resonance acceptance of a carboxyacyl than a phosphoryl substituent with respect to the non-bonding electrons of an adjacent nitrogen atom, renders the nitrogen atom of a mixed imide less basic than that of a symmetrical phosphoric imide. Therefore, the difference in the solvolytic behaviour of these two systems cannot be rationalised in terms of nitrogen atom basicity. Protonation of a phosphoric imide such as (7.8) results in the formation of an internally stabilised quasiphosphonium ion (7.17). As

discussed in Chapter 5, the analysis of the electron impact-induced fragmentation pattern of (7.8) has revealed the extremely high inherent stability of ions of this type in the gas phase (Scheme 5.10). Ions such as (7.17) may be subject to extensive "salting-in" in aqueous acidic media. Nucleophilic attack at either phosphoryl centre and subsequent P(O)-N hydrolysis via a pentacoordinate transition state or intermediate, would result in the loss of considerable resonance stabilisation and solvation energy and is thus, a disfavoured, high-energy process. By analogy, the relatively high stability of the monoanionic form of (7.15) at pH 4[24d] may be attributed to the formation of the stable, zwitterionic structure (7.15A) that is incapable of facile unimolecular expulsion of the diphenylphosphoramide leaving group.



(7.17)



(7.15A)

In contrast, the unsymmetrical conjugate acid derived from a mixed imide, has predominant charge localisation within the carboxamide moiety. As a result, the attendant loss of resonance energy and solvent reorganisational demands associated with nucleophilic attack at the phosphacyl centre of a conjugate acid such as (7.13), are relatively low, thus facilitating the direct displacement of the iminol leaving group.

This study has unambiguously demonstrated the importance of N-protonation in activating a phosphylamide towards nucleophilic solvolysis. However, the persistence of acid-catalysed P(O)-N solvolysis (albeit at a reduced rate) in systems in which the appropriate structural modifications preclude

N-protonation, illustrates that although it may be a sufficient condition, protonation at nitrogen is not a necessary condition for acid-catalysed P(O)-N solvolysis.

b. Nitrogen-Carbonyl Cleavage

Application of eq. 7.9 to the acid-catalysed N-C(O) hydrolyses of (1d) and (7.5a), reveals a slow step rate enhancement of the order of 10^5 - 10^6 upon introduction of an N-diethylphosphoryl substituent. Although the basicity constants of (7.9a,b) could not be determined, it is likely that the rate enhancements caused by N-carboxyacylation of an amide are even more pronounced. These results may be intuitively explained in terms of the relatively high carbonyl carbon electrophilicity in imide systems, thus facilitating the nucleophilic substitution process. The Zucker-Hammett approach was employed as a preliminary means of investigating and comparing the N-C(O) hydrolysis mechanisms of the substrates (1d), (7.5a) and (7.9a). The relationships between log k_ψ and both $-D_o$ and $-D_A$ are non-linear, with negative curvature, for all three substrates. However, log k_ψ is linearly dependent upon log C_D+ over an extensive acidity range for both the imide substrates (1d) and (7.9a) (Fig. 7.7, slopes 1.1 and 0.9 respectively),[207] indicating an A2 hydrolysis mechanism in both cases. However, in view of the limited mechanistic information obtainable from this treatment and its complete failure in the analysis of the rate-acidity dependence of (7.5a), the use of a more sophisticated treatment is obviously called for.

The Hydration Parameter Treatment

Yates and Stevens[188] have shown that the Brönsted rate equation for the generalised acid-catalysed hydrolysis reaction given in eq. 7.7, can be expressed as eq. 7.13a for weakly basic substrates, B, that are negligibly

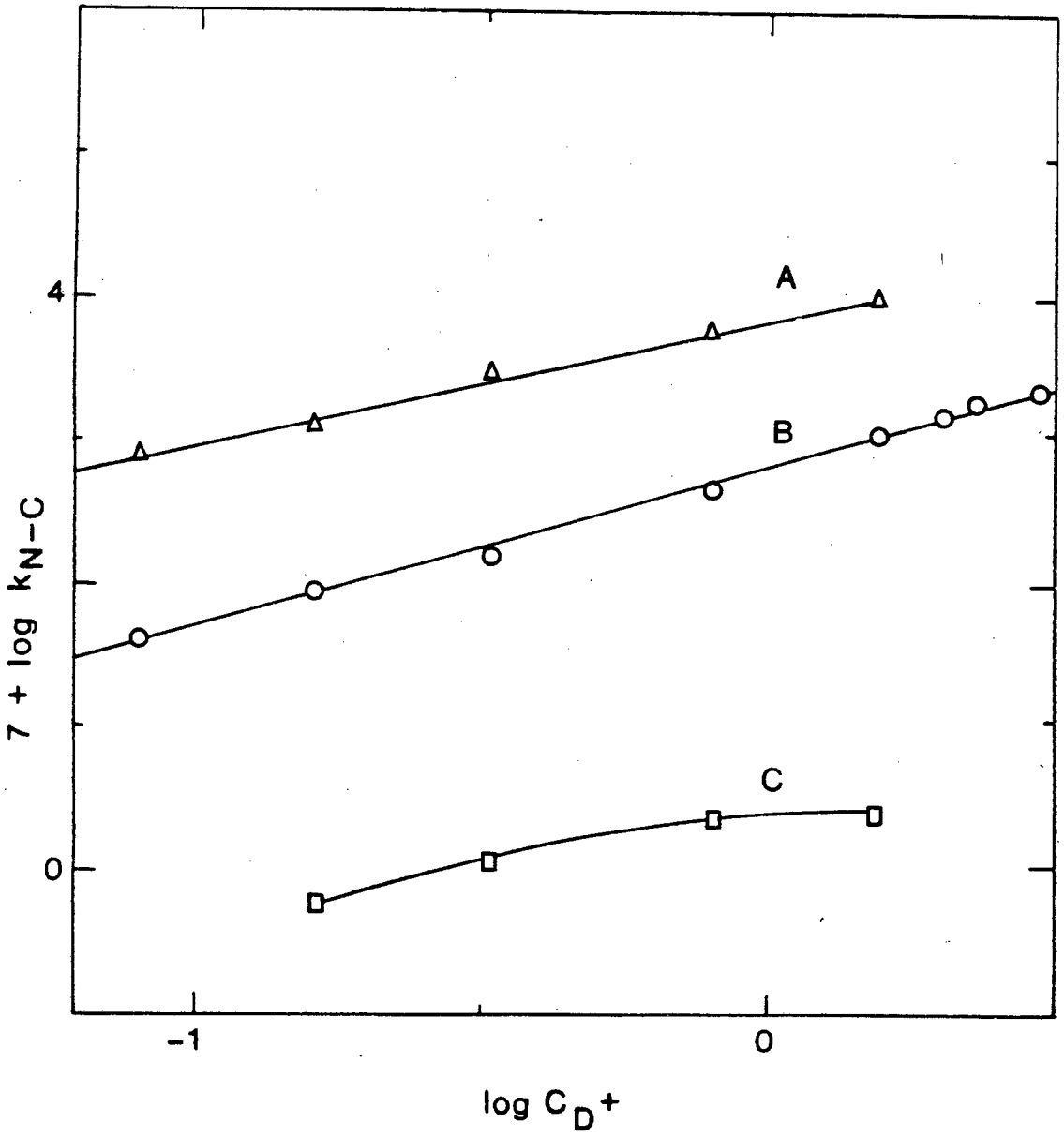


Figure 7.7 The Zucker-Hammett plots for the N-C(O) hydrolyses of: (A) (7.9a), —Δ— ; (B) (1d), —○— ; (C) (7.5a), —□—, in D_2O-D_2SO_4 mixtures at 25°C.

protonated in the reaction medium and, as eq. 7.13b for cases in which appreciable protonation occurs:

$$\log k_{\psi} + H_B = r \log a_{H_2O} + \text{constant} \qquad [7.13a]$$

$$\log k_{\psi} - \log\left[\frac{h_B}{h_B + K_{BH^+}}\right] = r \log a_{H_2O} + \text{constant} \qquad [7.13b]$$

H_B is an acidity function strictly appropriate to the base under consideration and the quantity r is an approximate measure of the hydration change accompanying the transformation of the protonated substrate to the transition state, which, in the case of an amide hydrolysis, corresponds to the rate-determining step. The above treatment and an equivalent r-parameter treatment[209] have been extensively applied to the hydrolyses of amides,[182,188,202,203] esters,[187] and lactams;[181] A2 mechanisms are typified by r-values between 2 and 4, whereas lower, negative r-values (-0.2 to -0.6) are indicative of an A1 hydrolysis mechanism.

As discussed above, the protonation behaviour of the mixed imide (1d) corresponds to that of a weakly basic carboxamide ($D_A\frac{1}{2}$ = -3.49), with appreciable protonation requiring acidities in excess of 50% D_2SO_4. In view of the adequate description of the ionisation behaviour of (1d) in D_2O - D_2SO_4 mixtures by the acidity function $D_B = 0.95\ D_A$ (Fig. 7.5 and Table 7.8), eq. 7.14a was applied to treat the medium dependence (up to 45% D_2SO_4) of its N-C(O) hydrolysis.

$$\log k_{\psi(N-C)} + 0.95\ D_A = r \log a_{D_2O} + \text{constant} \qquad [7.14a]$$

The least squares r-plot is shown in Fig. 7.8.[210] In dilute acid, the concentration of "free" water available for solvation is high and the average hydration numbers of the various species may differ substantially from those

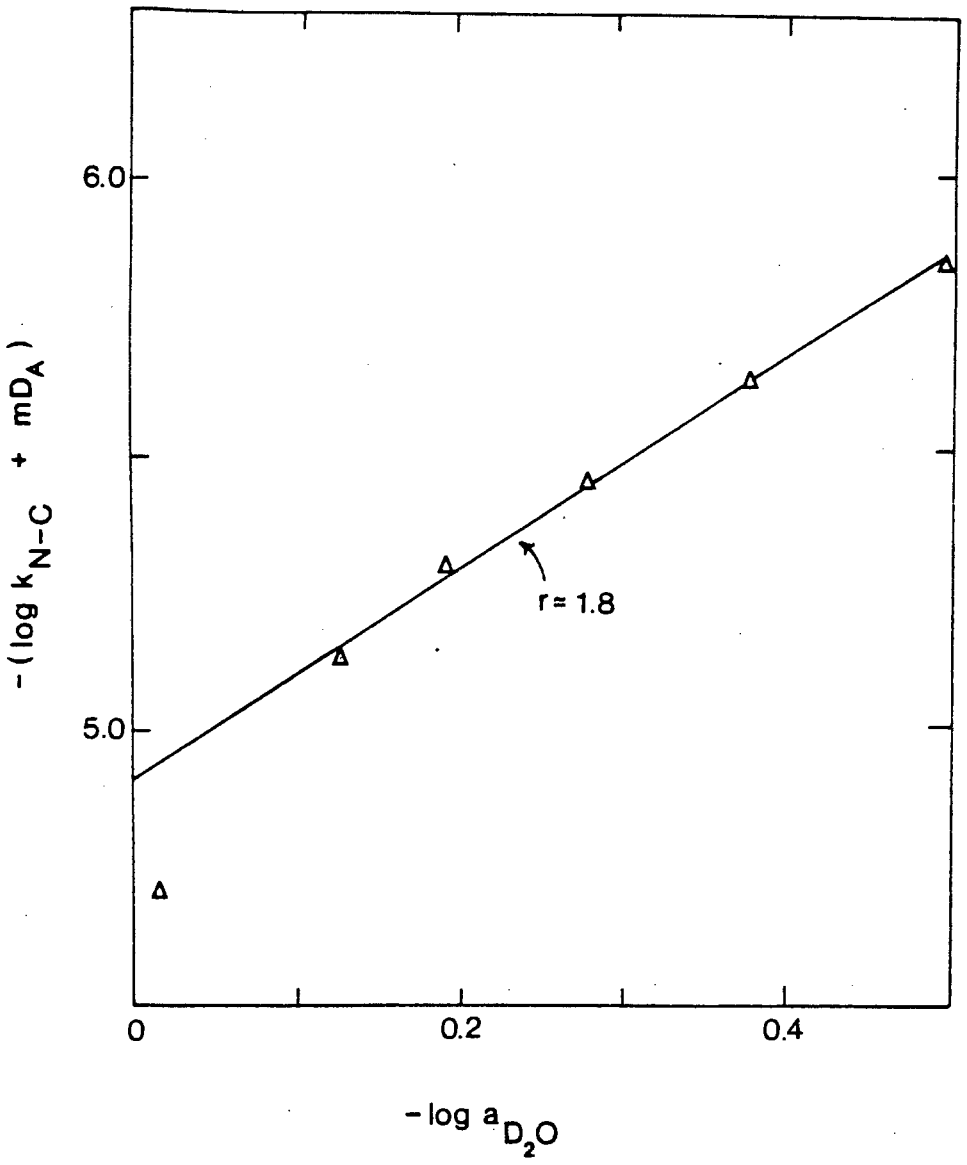


Figure 7.8 Application of the Hydration Parameter Treatment (eq. 7.14a) to the N-C(O) hydrolysis of (1d) in D_2O-D_2SO_4 mixtures at 25°C.

in the more concentrated media. The deviating point in dilute acid was thus omitted for the purpose of slope (r) evaluation. The plot of slope 1.76 indicates that conversion of the conjugate acid (7.13) to the transition state involves the participation of two D_2O molecules. In contrast, application of the same treatment to the acidic hydrolysis of weakly basic amides, such as picolinamide, in H_2O - HCl mixtures (eq. 7.13a, $H_B = H_A$) has yielded significantly higher r-values, of average 3.5.[202] Taking cognisance of the fact that r-values obtained for aqueous HCl hydrolyses, can be of the order of 10 - 25% higher than the analogous aqueous H_2SO_4 values,[212] it is quite obvious that the value of 1.76 for the N-C(O) hydrolysis of (1d) is nonetheless, unusually low.

The hydration plot for the N-C(O) hydrolysis of (1d) was extended to include the rate-acidity dependence in more strongly acidic media, by applying the more generalised treatment given in eq. 7.14b:

$$\log k_{\psi(N\text{-}C)} - \log \left[\frac{d_A^{\,m}}{d_A^{\,m} + K_{BD^+}^{\,m}} \right] = r \log a_{D_2O} + \text{constant} \qquad [7.14b]$$

In addition, the same treatment was applied in analysing the medium dependence of the hydrolysis of (7.5a), with the aim of directly assessing the effect of an N-diethylphosphoryl substituent upon the order of the slow step of the acetamide hydrolysis with respect to D_2O. The least squares hydration plots are illustrated in Fig. 7.9.

The hydration plot of (7.5a) consists of two straight line regions with a change of slope from 3.5 to 0.6 occurring at *ca.* 40% D_2SO_4. Wan *et al.*[181] have reported an analogous slope change in the hydration plot for the hydrolysis of N-ethylacetamide in H_2O - H_2SO_4 mixtures. Changes of this type are indicative of a mechanistic shift from a highly hydrated A2 mechanism in the low acidity region, incorporating at least three water

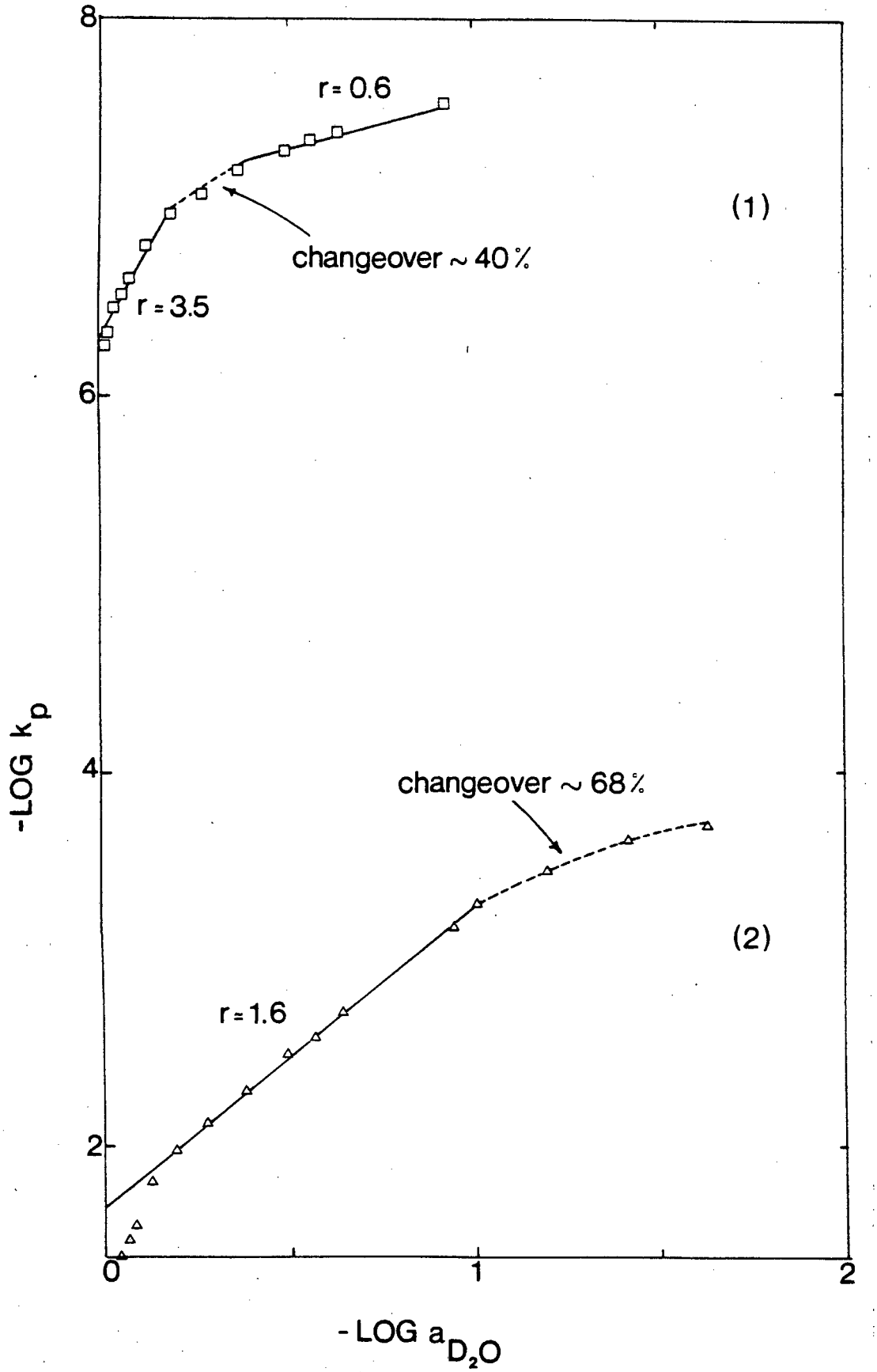
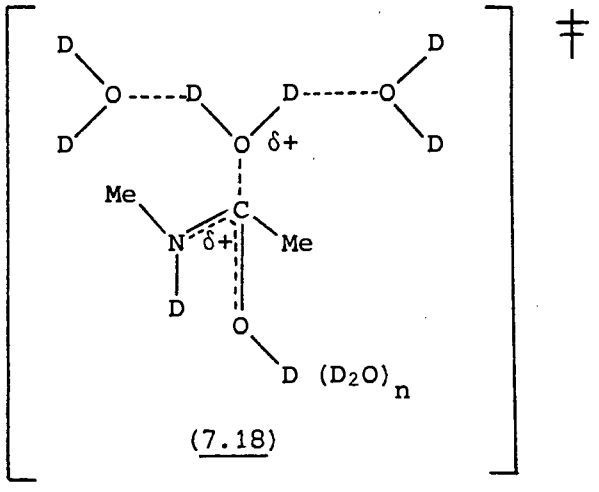


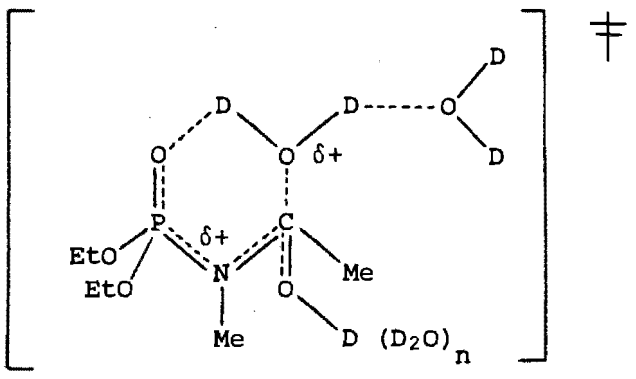
Figure 7.9 The Hydration Plots (eq. 7.14b) of: (1) (7.5a), — □ —; (2) (1d), — △ —; $\log k_p = \log k_{\psi(N-C)} - \log \left[d_A^m / (d_A^m + K_{BD^+}^m) \right]$.

molecules in the transition state formation, to a mechanism involving the participation of only one water molecule in the rate-determining step. Therefore, at all acidities, one water molecule is required for nucleophilic attack at the carbonyl centre. In the lower acid region (<40% D_2SO_4) the additional two water molecules serve to solvate the transition state by charge-dispersal to the medium, yielding a transition state structure such as (7.18):[213]



(7.18)

In contrast, the hydration plot for the hydrolysis of (1d) shows a single straight line relationship of slope 1.6, extending to *ca.* 65% D_2SO_4, beyond which, slight curvature is apparent; as above, the curvature may signify a mechanistic changeover at this acidity. The relatively high acidity at which the break in the hydration plot occurs, is largely a consequence of the relatively weak basicity of this substrate.[214] The unusually low slopes of the hydration plots of (1d) (Figs. 7.8, 7.9) indicate the formation, even in the low acidity media, of a relatively poorly hydrated transition state, incorporating at most two water molecules. The low hydration requirement of the transition state may be attributed to the participation of the phosphoryl group in intramolecular solvation of the transition state, to yield the structure (7.19), thus obviating the need for an additional solvating water molecule.



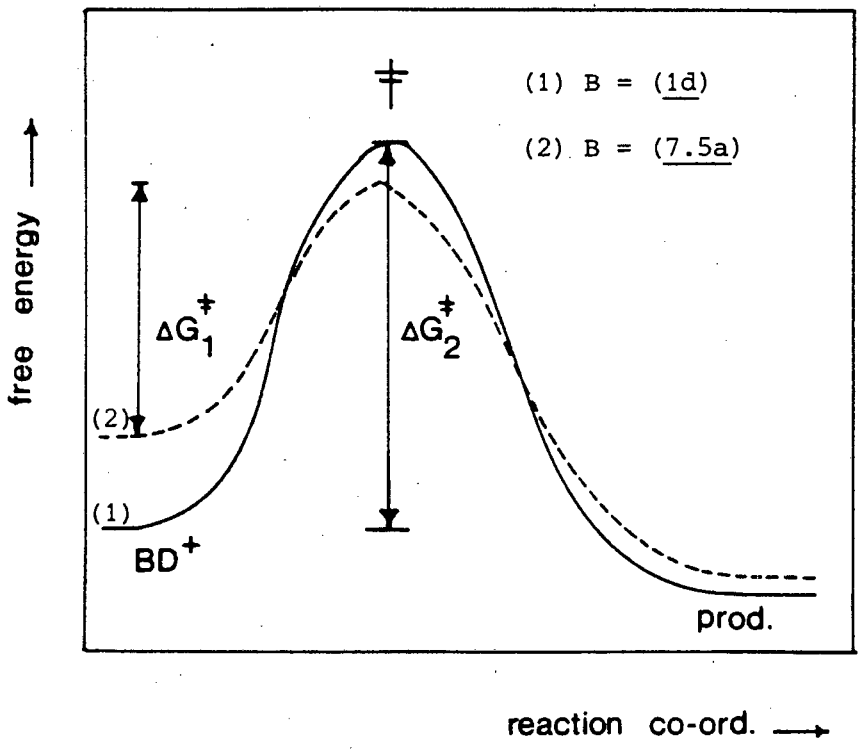
(7.19)

Although the hydration treatment could not be applied to the N-C(O) hydrolysis of the imides (7.9a,b), the analogous participation of the second carboxy-acyl substituent in intramolecular stabilisation is possible. An important implication of the formation of an internally stabilised structure, such as (7.19) in the acidic hydrolysis of an N-acyl carboxamide, is the relatively advanced stage of proton transfer to the leaving group in the rate-determining transition state. Since protonation of the leaving group must necessarily precede its departure, this type of "premature" proton transfer may accelerate the collapse of the tetrahedral intermediate to the hydrolysis products.

The dependence of the observed rate of N-C(O) hydrolysis of X-NMe-COMe upon the nature of substituent X, is illustrated in Table 7.8. The rate of hydrolysis clearly responds to the resonance-accepting ability of X (see Chapter 3), despite the concomitant reduction in carbonyl oxygen basicity. Owing to the resonance-stabilised, salted-in nature of the O-protonated conjugate acid of a carboxamide, the activation energy ($\Delta G^{\ddagger}$) for the transition state formation, is necessarily high. In contrast, the carbonyl oxygen-protonated conjugate acid of an imide (mixed or carboxylic) is severely destabilised by the resonance acceptance of the N-acyl substituent and is thus, brought much closer in free energy to its corresponding transition state. From the available pK_a and rate data for (1d) and (7.5a), it can

be estimated that the introduction of an N-diethylphosphoryl substituent lowers the free energy of activation of the N-C(O) hydrolysis step by a value, $\Delta\Delta G^{\ddagger}$, of the order of 40 kJ. (Fig. 7.10).

Figure 7.10



A similar argument has been invoked to account for the faster rate of acid-catalysed hydrolysis of a carboxylic ester than its amide analogue, despite the significantly weaker basicity of the former.[182] A comparative analysis of the rates of amide, imide and ester hydrolyses (Table 7.10) effectively illustrates the response of the observed hydrolysis rate to the electron-donating ability of the group X. These results suggest the existence of a "continuum" of A2 hydrolyses of carboxylic acid derivatives RC(O)-X, with the position of a given hydrolysis reaction along the continuum, being largely dictated by the influence of X upon the stability of the conjugate acid $[RC(OH)X]^+$.

Table 7.10 Rates of acidic hydrolysis of MeC(O)-X at 25°C.

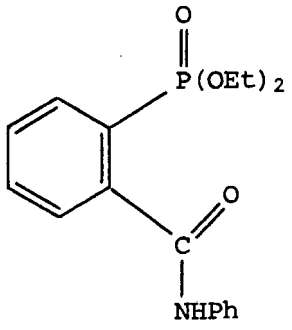
Substrate	X	$10^6 k_\psi (s^{-1})$ 10%	15%	20%	25% acid
(7.5a)	NDMe	0.23	1.70	0.24	0.18
(1f)	$NMePOEt_2$	7.6	12.6	18.2	23.4
(1d)	$NMePO(OEt)_2$	18.2	31.6	138	178
(7.20)[a]	OMe	167	267	450	567
(7.9a)	NMeC(O)Me	708	1096	1514	1950

[a] The rates of hydrolysis of $MeCO_2Me$ (7.20) in H_2O - H_2SO_4 mixtures are taken from Ref. 187b.

It is of interest to note that there is no trace whatsoever of ester solvolysis of the phosphoric substrates (1a-e) (via either P-O or C-O cleavage) under neutral and acidic conditions. As discussed above, the most likely mechanism for the neutral P(O)-N solvolysis of (1c-e,g) involves the formation of an oxyphosphorane intermediate (Scheme 7.2), with proton transfer to the carboxamide moiety and subsequent pseudorotation of the intermediate preceding the cleavage step. Phosphate ester solvolysis via P-O bond cleavage would require prior proton transfer to the ester oxygen, followed by departure of the neutral alcohol. Despite the comparable basicities of aliphatic alcohols and carboxylic amides,[206] the cleavage preference of the P^V intermediate indicates that proton transfer to the carbonyl oxygen via a six-membered transition state is favoured over proton transfer to the ester oxygen via a four-membered transition state. In addition, the absence of dealkylation under neutral conditions is indicative of preferential nucleophilic attack by the solvent at the phosphorus rather than the ester carbon atom.

Kluger *et al.*[215] have observed intramolecular nucleophilic catalysis by the

adjacent carboxamide moiety in the acidic hydrolysis of the phosphonate esters (7.21) and (7.22) and comparison with related systems has revealed that the internal nucleophile has an "apparent molarity" of the order of 10^3-10^6 M.



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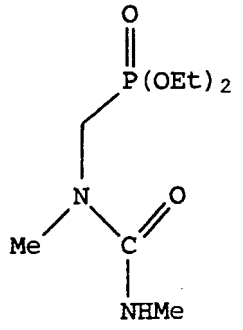
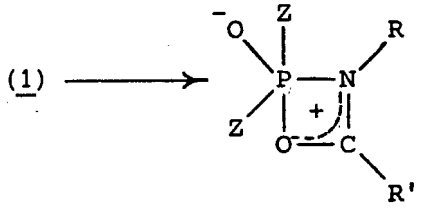


(7.22)

The proposed hydrolysis mechanism[215] involves rapid attack by the carbonyl oxygen atom at the phosphonyl centre, to yield a P^V intermediate which releases ethanol after the appropriate proton transfer step. The involvement of analogous intramolecular nucleophilic participation in the solvolysis of the mixed imide system (1) would require the formation of the intermediate (7.23) containing a four-membered ring (eq. 7.15):



[7.15]

(7.23)

The geometrical constraint associated with the formation of (7.23) is much higher than the analogous cyclisation of the phosphonates (7.21) and (7.22), thereby effectively excluding the participation of the carbonyl oxygen of (1) as an intramolecular nucleophile in the solvolysis reactions conducted at 25°C. The role of the carbonyl oxygen atom in the solvolysis of (1) under neutral and acidic conditions is therefore limited to that of a proton acceptor.

CHAPTER 8

Conclusions

The attempts to develop procedures for the synthesis of tertiary N-acyl phosphylamides, have raised a number of intriguing mechanistic questions concerning the phosphylation reactions of carboxamides and the acylation reactions of phosphylamides. The participation, and attendant structural dependence of the side reactions that plague the N-phosphylation of an N-substituted carboxamide anion as a synthetic route to the corresponding mixed imide, have been tentatively ascribed to the ambident nucleophilic character of the anion. Parallel formation of the highly reactive O-phosphyl imidate isomer may lead to the introduction of new, reactive species, from which by-products arise. The acylation reaction of a phosphylamide under both basic and acidic conditions, is a totally unsatisfactory means of mixed imide preparation, leading instead to the corresponding carboxylic amide and imide products, via an apparent nitrogen group transfer process. The mechanistic aspects of the phase transfer-catalysed reaction of the conjugate base of N-methyl diethylphosphoramidate with benzoyl chloride, are currently under further investigation in this laboratory,[232] with particular attention being paid to the possibility of mixed imide intermediacy in the phosphylamide → carboxamide transformation.

An analysis of the spectroscopic, structural and chemical properties of the mixed imide system, has revealed an unsymmetrical Π-electron distribution within the OPNCO fragment, being weighted in favour of resonance interaction between the nitrogen non-bonding electrons and the adjacent carboxyacyl centre. This conjugational preference is in agreement with independently reached conclusions based on studies of the individual phosphylamide and carboxamide systems,[11,12] and results in relatively high electron density at the carbonyl oxygen atom. However, comparative bond length, IR and NMR analyses have revealed that the electron-withdrawing ability of a phosphyl substituent is nonetheless significant, rendering substantial "imidic"

character to this mixed diacylamine system. Conjugation of the nitrogen non-bonding electrons with both acyl centres provides a strong driving force towards nitrogen atom planarity, as indicated by the molecular structure of (1a). The resultant significant weakening in nucleophilicity of the nitrogen atom is reflected in the inability to achieve N-ethylation of the conjugate base of N-benzoyl dimethylphosphoramidate. Moreover, comparative solvolytic studies have revealed the effective elimination of the nitrogen atom as a competitive basic centre, by virtue of its imidic character.

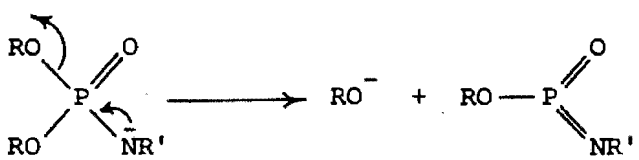
The relative electron-richness of the carbonyl oxygen atom manifests itself in a variety of ways, one of which is in the nucleophilic behaviour of the conjugate base of (1a), with a clear preference for carbonyl oxygen ethylation being displayed. In addition, it accounts for the ionisation and solvolytic behaviour of (1d) in acidic media, with carbonyl oxygen protonation activating the N-C(O) bond, but deactivating the P(O)-N bond towards nucleophilic solvolysis.

The adoption of a *cis-trans* conformation by the essentially planar OPNCO mixed imide moiety, positions the electron-rich carbonyl oxygen atom directly beneath one of the tetrahedral faces of the phosphyl centre. Structural studies have shown that the non-bonded $C{=}O....P^{IV}$ distance in the *cis-trans* geometry of (1a) is sufficiently close to favourably dispose the molecule towards intramolecular nucleophilic displacement. Attempts are currently underway in this laboratory[233] to determine the molecular and crystal structure of the cyclic, tertiary mixed imide (1g), with the aim of establishing whether incorporation of the phosphorus atom into a strained, five-membered ring, encourages an even more pronounced approach of the nucleophilic carbonyl oxygen atom towards the phosphyl centre, in order to alleviate unfavourable ring strain.

The adequately demonstrated propensity of the N-acyl phosphylamide system towards isomerisation to the corresponding O-phosphyl imidate system, the prelude to which is *cis-trans* conformational constraint, adds a new and fascinating dimension to the chemistry of this class of compounds.

In conclusion, it is clear that a full understanding and description of the structural and chemical properties of the mixed imide system (1) is far from completion. The major research directions that are currently being followed in order to obtain greater insight into the mutual interactions of the carbonyl and phosphacyl groups, are indicated below:

1. The nucleophilic behaviour of phosphoramidate conjugate bases. During the course of investigating the acylation reactions of anions (8.1), it has been found that these electron-rich anions are also capable of undergoing unimolecular collapse, releasing alkoxide ions and generating highly reactive, metaphosphorimidate intermediates (eq. 8.1):



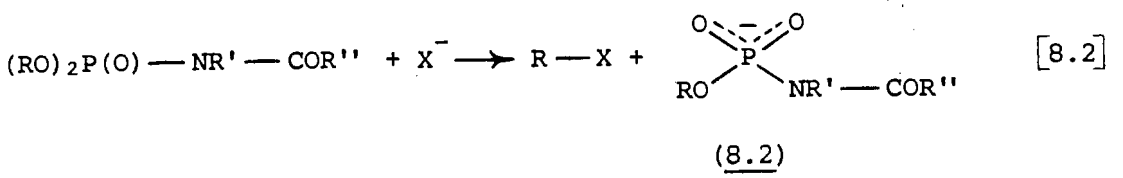
[8.1]

(8.1)

The competition between the reaction given by eq. 8.1 and the direct condensation process of (8.1) with the acylating agent, offers an example of the unimolecular vs. bimolecular reactivity of a reactive species and provides a key to understanding the synthetic difficulties associated with the preparation of compounds (1; Z = RO, R = Me).

2. Nucleophilic attack at the ester carbon of (1; Z = RO). As mentioned above (Chapter 7), no evidence was found for the solvolysis of (1) via P(O)-OR bond cleavage. However, the dealkylation reaction of (1) has been achieved by using bromide and chloride ion nucleophiles, which selectively

attack the alkyl carbon atom to yield the highly reactive anion (8.2) (eq. 8.2):



[8.2]

(8.2)

The anion (8.2) is, itself, capable of unimolecular expulsion of the RO^- and/or $[R''CONR']^-$ anions and investigation of its reactivity offers an opportunity of analysing elimination preferences in processes involving metaphosphate-type intermediate formation.

3. Molecular orbital calculations are currently being performed on compounds (1), their O-phosphyl imidate isomers and their conjugate bases, with the aim of correlating the observed chemical behaviour of (1) (and related systems) with the computed structural parameters, conformational preferences, charge densities and activation energies associated with selected chemical transformations.

The preliminary results of topics 1 - 3, although promising and interesting, have not been included in this dissertation by virtue of their incompleteness.

CHAPTER 9

Experimental

9.1 GENERAL

^{1}H NMR spectra were recorded on a 100 MHz Varian XL100 spectrometer with tetramethyl silane (TMS) as internal reference. ^{13}C NMR spectra were recorded on a Bruker WH90 spectrometer operating in the FT mode, with TMS as internal reference. Infrared spectra were recorded on a Perkin Elmer 180 spectrophotometer at 33°C using CsI plates. Mass spectra were recorded on a VG Micromass 16F spectrometer. Gas chromatographic analyses were performed on a Hewlett Packard HP5710 A model fitted with a 12.4 m x 0.39 mm glass capillary packed with Silar 10 C on barium carbonate. A Haake D1 thermostat and Haake L water bath were used for kinetic studies. Melting points (uncorrected) were recorded on a Fisher-Johns m.p. apparatus. Solvents were removed under reduced pressure using a Büchi rotary evaporator equipped with a Kotterman water bath. Aluminium-backed silica gel plates (Merck, Kieselgel $60F_{254}$, Art. 5554) were used for thin-layer chromatography. Column chromatography was carried out on silica gel columns (Merck, Kieselgel 40, Art. 10180, 70 - 230 mesh ASTM; Kieselgel 60, Art. 9385, 70 - 230 mesh ASTM).

All analyses for C, H and N were carried out at the University of Cape Town by Mr. W.R.T. Hemsted.

9.2 REAGENTS

AnalaR acetone, ethyl acetate, diethyl ether, ethanol, methanol, dichloromethane, chloroform, carbon tetrachloride, benzene, toluene and petroleum ether were used as supplied and dried (where applicable) according to standard procedure. Aldrich Gold Label d^6-acetone, d^6-dimethylsulfoxide, d-chloroform, d^4-methanol, deuterium oxide and deuteriosulfuric acid were used as supplied.

Phosphorus trichloride, sulfuryl chloride, benzoyl chloride, thionyl chloride, aniline, pyridine (Merck), 1,2-ethanediol, chloroacetone (BDH), ethyl iodide, ethyl bromide (M & B) and diethyl phosphorochloridate (Fluka) were distilled before use.

Isopropenyl acetate, N-methylacetamide, trimethyl phosphite, triethyl phosphite, p-toluene sulfonic acid, sulfuric acid, aluminium trichloride, sulfur flowers, potassium carbonate, magnesium sulfate, iodine, phosphorus pentachloride (Merck), aqueous methylamine, sodium hydride, silver acetate (BDH), tetra-n-butylammonium bromide, boron trifluoride etherate and triethyloxonium tetrafluoroborate (Fluka) were used as supplied.

9.3 SUBSTRATES

Dimethylphosphorochloridate.[216] To a cold, stirred solution of 61 cm^3 dry MeOH in 150 cm^3 dry benzene, is added a solution of 44 cm^3 freshly distilled PCl_3 in 44 cm^3 dry benzene dropwise with stirring over 1 h, at a temperature of 5 - 10°C. Freshly distilled SO_2Cl_2 (41 cm^3) is then added dropwise to the mixture which is left to stand overnight. The benzene is removed under reduced pressure and the remaining product purified by distillation. 73% yield, b.p. 25 - 26°C (0.03 mm) (lit.[216] b.p. 55 - 57°C (2 - 3 mm)).

Diphenylphosphinchloridate.[217] A mixture of Ph_2PO_2H (0.114 mol) and 47 cm^3 freshly distilled $SOCl_2$ is heated under reflux for 45 min, then attached to a water pump and heated at 120°C for 3 h to remove the HCl and SO_2 produced. The pale yellow liquid is purified by distillation. 86% yield, b.p. 167 - 168°C (0.2 mm) (lit.[217] b.p. 160 - 162°C (0.15 mm)).

Diethylphosphinchloridate.[218] (1) A mixture of freshly distilled PCl_3 (0.75 mol), dry powdered sulfur (0.75 mol) and freshly sublimed $AlCl_3$ (0.015 mol) is gently warmed (40 - 50°C) to dissolve the $AlCl_3$. A spontaneous, vigorous reaction follows, which requires efficient cooling until all the sulfur disappears, leaving a yellow liquid. The product, phosphorus sulfochloride ($PSCl_3$) is purified by distillation. 76% yield, b.p. 122°C (lit.[218a] b.p. 122 - 123°C).

(2) A solution of $PSCl_3$ (0.31 mol) in 100 cm^3 dry ether is added during 3 - 4 h with stirring and cooling to a solution of Grignard reagent prepared from Mg (0.90 mol) and freshly distilled EtBr (0.90 mol) in 300 cm^3 dry ether, maintaining the temperature at 10 - 15°C. The mixture is magnetically stirred overnight and then heated on a water bath for 1 h. A sufficient volume of 10% H_2SO_4 to produce two distinct layers is then added to the mixture; the ether layer is separated and dried over anhydrous $MgSO_4$ and the ether removed to leave a white solid. The product, tetraethyl diphosphine disulfide $(Et_2PS)_2$, is purified by suspension in 30 cm^3 MeOH, filtration and recrystallisation from aqueous acetone. 63% yield, m.p. 73 - 75°C (lit.[218b] m.p. 76 - 77°C).

(3) To a solution of $(Et_2PS)_2$ (0.041 mol) in 31 cm^3 dry benzene, is added a solution of freshly distilled SO_2Cl_2 (0.126 mol) in 21 cm^3 dry benzene, dropwise with stirring and cooling. The solution is decanted over the precipitated sulfur and the benzene, $SOCl_2$ and SO_2 are removed under reduced pressure, leaving a pale yellow oil. The product, Et_2POCl, is purified by distillation. 86% yield, b.p. 56 - 59°C (0.5 mm) (lit.[218c] b.p. 64°C (0.5 mm)).

Ethylenephosphorochloridate (2-Chloro-2-oxo-1,3,2-dioxaphospholane).[219]

(1) To a stirred solution of 22 cm^3 freshly distilled PCl_3 in 50 cm^3 dry CH_2Cl_2 is added 13.9 cm^3 freshly distilled 1,2-ethanediol at such a rate as to allow gentle heating under reflux. The mixture is stirred at room temperature for 1.5 h, evaporated and the crude 2-chloro-1,3,2-dioxaphospholane purified by distillation, b.p. 44 - 46°C (12 mm) (lit.[219a] b.p. 45.5 - 47°C (15 mm)).

(2) The product is then dissolved in dry benzene and a stream of dry oxygen is bubbled through the solution for a period of 8 h. The solvent is removed under reduced pressure and the product (ethylene phosphorochloridate) is purified by distillation. 42% overall yield, b.p. 96 - 98°C (0.5 mm) (lit.[219b] b.p. 79°C (0.4 mm)).

N-Methyl dialkylphosphylamidates, $Z_2P(O)NHMe$. An excess of dry methylamine (*ca.* 0.2 mol) is bubbled into a stirred, cooled (0 - 5°C) solution of $Z_2P(O)Cl$ (0.05 mol) in 100 cm^3 dry ether. The methylammonium chloride precipitate is filtered and the filtrate evaporated under reduced pressure leaving the crude product which is purified by distillation or crystallisation.

Z = MeO: 78% yield, b.p. 66 - 68°C (0.1 mm) (lit.[17] b.p. 81°C (1mm)). ^1H NMR ($CDCl_3$): δ 2.58 (3H, d of d, $PNCH_3$, $J_{H,H}$ 6 Hz, $J_{H,P}$ 13 Hz); 3.71 (3H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 4.0 (1H, broad s, NH). Anal. calc. for $C_3H_{10}NO_3P$: C, 25.90; H, 7.25; N, 10.07%. Found: C, 25.80; H, 7.20; N, 10.0%.

Z = EtO: 75% yield, b.p. 92°C (0.3 mm) (lit.[220] b.p. 130°C (15 mm)). ^1H NMR ($CDCl_3$): δ 1.35 (6H, t, β-CH_3, $J_{H,H}$ 7 Hz); 2.59 (3H, d of d, $PNCH_3$, $J_{H,H}$ 6.5 Hz, $J_{H,P}$ 12 Hz); 4.06 (4H, m, α-CH_2); 3.40 (1H, broad s, NH). Anal. calc. for $C_5H_{14}NO_3P$: C, 35.93; H, 8.44; N, 8.38%. Found: C, 35.80; H, 8.45; N, 8.20%.

Z = Et: 42% yield, b.p. 129 - 131°C (0.5 mm). ^{1}H NMR ($CDCl_3$): δ 1.13 (6H, d of t, β-CH_3, $J_{H,H}$ 8 Hz, $J_{H,P}$ 18 Hz); 1.55 - 1.90 (4H, m, α-CH_2); 2.63 (3H, d, $PNCH_3$, $J_{H,P}$ 11 Hz); 3.30 (1H, broad s, NH). Anal. calc. for $C_5H_{14}NOP$: C, 44.43; H, 10.44; N, 10.37%. Found: C, 42.90; H, 9.85; N, 8.60%.

Z = Ph: 78% yield, m.p. 107 - 109°C (petroleum ether (60 - 80°)/benzene, 4:1). ^{1}H NMR ($CDCl_3$): δ 2.60 (3H, d, $PNCH_3$, $J_{H,H}$ 5 Hz, $J_{H,P}$ 13 Hz); 3.5 (1H, broad s, NH); 7.4 - 7.5 (6H, m, m-, p-aryl H); 7.8 - 8.0 (4H, m, o-aryl H). Anal. calc, for $C_{13}H_{14}NOP$: C, 67.52; H, 6.10; N, 6.06%. Found: C, 65.65; H, 6.0; N, 6.05%.

N-Phenyldimethylphosphoramidate.[65] To a stirred, cooled (0 - 5°C) solution of $(MeO)_2POCl$ (0.10 mol) and triethylamine (0.1 mol) in 100 cm^3 dry ether is added a solution of freshly distilled aniline (0.1 mol) in 10 cm^3 dry ether, dropwise over 1 h. The $Et_3\overset{+}{N}H\overset{-}{Cl}$ precipitate is removed by filtration and the filtrate evaporated under reduced pressure leaving a pale yellow solid which is purified by recrystallisation (pet. ether (60 - 80°C)/benzene, 10:1). The product turns dark green on exposure to light. 78% yield, m.p. 83 - 86°C (lit.[65] m.p. 84 - 85.5°C). ^{1}H NMR ($CDCl_3$): δ 3.79 (6H, d, $POCH_3$, $J_{H,P}$ 12 Hz); 6.9 - 7.4 (5H, m, aryl H); 7.8 (1H, broad s, NH). Anal. calc. for $C_8H_{12}NO_3P$: C, 47.76; H, 6.01; N, 6.96%. Found: C, 47.50; H, 5.95; N, 6.80%.

N-Methylbenzamide. An excess of dry methylamine is bubbled into a stirred cooled (0 - 5°C) solution of PhCOCl (0.28 mol) in 100 cm^3 dry benzene. The $Me\overset{+}{N}H_3\overset{-}{Cl}$ precipitate is removed by filtration and the benzene removed from the filtrate under reduced pressure, leaving a pale yellow solid. The product is dissolved in chloroform, washed with water (2 x 10 cm^3) and dried over anhydrous $MgSO_4$. The solvent is removed under reduced pressure leaving a white solid which is purified by recrystallisation. 75% yield,

m.p. 75 - 76°C (pet. ether (80 - 100°C)/acetone, 4:1) (lit.[221] m.p. 75°C). ^{1}H NMR ($CDCl_3$): δ 2.94 (3H, d, NCH_3, $J_{H,H}$ 5 Hz); 7.2 (1H, broad s, NH); 7.2 - 7.5 (3H, m, m-, p-aryl H); 7.82 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 7 Hz). Anal. calc. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.37%. Found: C, 70.85; H, 6.65; N, 10.25%.

N-Ethylbenzamide and O-Ethylbenzimidate. The phase transfer-catalysed reaction between $PhCONH_2$ and EtI is carried out by heating under reflux, a mixture of the amide (0.02 mol), TBAB (5 mol %) and excess EtI (0.2 mol) in a two-phase system of 50% NaOH (20 cm^3) and benzene (20 cm^3). After 6 h, the phases are separated and the benzene solution washed with water (2 x 20 cm^3), dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The product mixture is separated by column chromatography, eluting with 10% acetone in chloroform.

Fraction 1: O-ethylbenzimidate, 40% yield. ^{1}H NMR ($CDCl_3$): δ 1.35 (3H, t, CH_3); 4.33 (2H, q, CH_2, $J_{H,H}$ 7 Hz); 7.3 - 7.6 (4H, m, m-, p-aryl H and N-H); 8.05 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 7 Hz). Anal. calc. for $C_9H_{11}NO$: C, 72.50; H, 7.43; N, 9.39%. Found: C, 72.00; H, 7.40; N, 9.20%.

Fraction 2: N-ethylbenzamide, 42% yield, m.p. 67 - 68°C (lit.[222] m.p. 69°C). ^{1}H NMR ($CDCl_3$): δ 1.18 (3H, t, CH_3); 3.42 (2H, quintet, CH_2); 7.3 - 7.5 (4H, m, m-, p-aryl H and NH); 7.85 (2H, d of d, o-aryl H).

N-Acyl-N-methylacetamide, RCO-NMeAc.[40,223] A mixture of isopropenyl acetate (1 mol), carboxamide RCONHMe (0.3 mol) and 20 drops 96% H_2SO_4 in 40 cm^3 toluene, is heated under reflux for 20 h with stirring. Removal of the volatile materials (toluene, acetone, IPA) under reduced pressure leaves the crude product which is purified by distillation.

R = Me: 77% yield, b.p. 88 - 89°C (12 mm) (lit.[223] b.p. 71°C (7 mm)). ^{1}H

NMR ($CDCl_3$): δ 2.42 (6H, s, $COCH_3$); 3.22 (3H, s, NCH_3). Anal. calc. for $C_5H_9NO_2$: C, 52.16; H, 7.90; N, 12.16%. Found: C, 52.01; H, 7.90; N, 11.55%.

R = Ph: 72% yield, b.p. 90 - 93°C (0.02 mm). ^1H NMR ($CDCl_3$): δ 2.32 (3H, s, $COCH_3$); 3.21 (3H, s, NCH_3); 7.4 - 7.7 (5H, m, aryl H). Anal. calc. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91%. Found: C, 67.25; H, 6.30; N, 7.85%.

Dibenzimide.[224] To a stirred, cooled solution of $PhCONH_2$ (8 mmol) in dry pyridine (40 mmol) is added dropwise PhCOCl (8 mmol). The mixture is stirred at 20°C for 3 h and washed with water (20 cm^3); the oil that separates is extracted with ether (20 cm^3), washed with dilute H_2SO_4 to remove the last traces of pyridine and left to stand. The product is purified by column chromatography, eluting with 10% acetone in chloroform. 52% yield, m.p. 148 - 149°C (lit.[224] m.p. 144°C). ^1H NMR ($CDCl_3$): 7.3 - 7.6 (6H, m, m-, p-aryl H); 7.85 (4H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 8 Hz); 9.2 (1H, broad s, NH). Anal. calc. for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.10; H, 4.95; N, 6.05%.

Tetraethylpyrophosphate.[225a] A mixture of water (0.039 mol) and pyridine (0.079 mol) is added dropwise over 1 h to $(EtO)_2POCl$ (0.079 mol) with stirring and cooling (0 - 4°C). The mixture is stirred for 20 min., warmed with stirring to 35°C, stirred at 35°C for 20 min. and finally cooled to 0°C. The pyridinium hydrochloride is filtered and thoroughly washed with dry ether. The ether is removed under reduced pressure and the product purified by distillation. 89% yield, b.p. 109 - 111°C (0.01 mm) (lit.[225a] b.p. 138°C (1 mm)). Anal. calc. for $C_8H_{20}O_7P$: C, 33.05; H, 6.90%. Found: C, 33.11; H, 6.95%.

N-Methyl tetraalkylimidophosphate, $(RO)_2PO\text{-}NMe\text{-}PO(OEt)_2$. To a stirred suspension of $(EtO)_2PONNaMe$ prepared from $(EtO)_2PONHMe$ (12 mmol) and sodium hydride (12 mmol) and TBAB (5 mol %) in 20 cm^3 dry toluene, is added a solution of $(RO)_2POCl$ (12 mmol) in 5 cm^3 dry toluene dropwise over 30 min. The exothermic reaction is accompanied by the formation of a white foam; the mixture is heated under reflux with stirring for 12 h and the product isolated by column chromatography, eluting with chloroform / acetone, 1:1.

R = Me: 52% yield. ^1H NMR ($CDCl_3$): δ 1.38 (6H, t, β-CH_3, $J_{H,H}$ 7 Hz); 2.96 (3H, t, NCH_3, $J_{H,P}$ 9.5 Hz); 3.79 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 4.16 (4H, quintet, α-CH_2, $J_{H,P} = J_{H,H}$ 7 Hz).

R = Et: The fractions obtained by column chromatography were identified as follows:

First fraction: Triethylphosphate, 8% yield, formed via unimolecular expulsion of EtO^- from the phosphoramidate anion followed by reaction with $(EtO)_2POCl$.[226] δ 1.35 (3H, t, β-CH_3, $J_{H,H}$ 7 Hz); 4.12 (2H, quintet, α-CH_2, $J_{H,H} = J_{H,P}$ 7 Hz). MS: m/e 182 (M^+).

Second fraction: $[(EtO)_2PO]_2NMe$, 55% yield. ^1H NMR ($CDCl_3$): δ 1.38 (12H, t, β-CH_3, $J_{H,H}$ 7 Hz); 2.96 (3H, t, NCH_3, $J_{H,H}$ 9.5 Hz); 4.20 (8H, m, α-CH_2). Anal. calc. for $C_9H_{23}NO_6P_2$: C, 35.65; H, 7.65; N, 4.62%. Found: C, 35.55; H, 7.60; N, 4.55%.

Third fraction: Unreacted $(EtO)_2PONHMe$.

Dialkylisopropenylphosphate, $(RO)_2P(O)O(CCH_2)Me$.[227] A mixture of $P(OR)_3$ (0.1 mol) and freshly distilled $ClCH_2Ac$ (0.1 mol) is heated for 4 h at 90 - 100°C (R = Me) or 100 - 110°C (R = Et) until the evolution of EtCl is complete. The crude product is purified by distillation.

R = Me: 78% yield,[228] b.p. 50 - 51°C (0.04mm)(lit.[227] b.p. 84 - 86°C (10 mm)). ^1H NMR ($CDCl_3$): δ 1.97 (3H, s, CH_3); 3.83 (6H, d, $POCH_3$, $J_{H,P}$ 12 Hz);

4.51 (1H, broad s, vinyl H); 4.76 (1H, broad s, vinyl H). MS: m/e 166 (M^+), 127 (base, $M-C_3H_3^{\cdot}$). Anal. calc. for $C_5H_{11}O_4P$: C, 36.15; H, 6.68%. Found: C, 36.05; H, 6.65%.

R = Et: 82% yield,[228] b.p. 55 - 57°C (0.15 mm) (lit.[227] b.p. 77 - 78°C (3 mm)). ^1H NMR ($CDCl_3$): δ 1.37 (6H, t, β-CH_3, $J_{H,H}$ 7 Hz); 1.97 (3H, s, CH_3); 4.18 (4H, quintet, α-CH_2, $J_{H,H} = J_{H,P}$ 7 Hz); 4.52 (1H, broad s, vinyl H); 4.78 (1H, broad s, vinyl H). MS: m/e 194 (M^+). Anal. calc. for $C_7H_{15}O_4P$: C, 43.30; H, 7.79%. Found: C, 43.25; H, 7.75%.

1-Diethylphosphonyl-2-oxo-propane.[229]

(1) Iodoacetone:[230] To a stirred suspension of isopropenyl acetate (0.062 mol) and silver acetate (0.063 mol) in 100 cm^3 dry chloroform is added a solution of iodine (0.063 mol) in 100 cm^3 dry chloroform, dropwise over 2 h. The mixture is stirred at 18 - 20°C for 24 h. The AgI is removed by filtration and the yellow filtrate evaporated under reduced pressure to yield the crude product which is purified by distillation. 56% yield, b.p. 57 - 59°C (10 mm) (lit.[231] b.p. 62°C (12 mm)).

(2) Perkow reaction: To a stirred solution of ICH_2Ac (0.03 mol) in 20 cm^3 dry ether is added $P(OEt)_3$ (0.03 mol) dropwise over 1 h. The mixture is stirred at 36°C for a further 2 h and the ether removed under reduced pressure, leaving the crude product which is purified by distillation. 63% yield, b.p. 63 - 65°C (0.3 mm) (lit.[229] b.p. 127 - 129°C (10 mm)). ^1H NMR ($CDCl_3$): δ 1.33 (6H, t, β-CH_3); 2.31 (3H, s, $COCH_3$); 3.08 (2H, d, J(PCH) 23 Hz); 4.14 (4H, quintet, α-CH_2, $J_{H,H} = J_{H,P}$ 7 Hz).

N-Benzoyldialkylphosphoramidates (1a,b).[15]

Part 1: A mixture of PCl_5 (0.065 mol) and $PhCONH_2$ (0.066 mol) in 15 cm^3 carbon tetrachloride is rapidly warmed to 50 - 60°C. The vigorous reaction in which HCl is evolved is completed by heating the mixture at 60 - 70°C on

a water pump for 1 h. To the cloudy yellow liquid residue is added 10 cm^3 petroleum ether (60 - 80°C) and the mixture heated under reflux for 15 min. and finally allowed to stand overnight. The white solid product, N-benzoyl trichlorophosphorimidate, is collected by filtration and dried *in vacuo* over silica gel; 57% yield.

Part 2: To a cooled solution of NaOR (0.149 mol; R = Me, Et) in 5 cm^3 dry ROH is added $PhCON{=}PCl_3$ (0.037 mol) in small portions. The alcohol is removed under reduced pressure and the white solid residue dissolved in a minimal amount of water. The solution is filtered and the filtrate acidified by adding dilute HCl dropwise.

R = Me (1a): The white precipitate formed is immediately filtered, washed with water and dried *in vacuo* over silica gel. 85% yield, m.p. 117 - 118°C (lit.[15] m.p. 116 - 117°C). ^1H NMR ($CDCl_3$): δ 3.90 (6H, d, $POCH_3$, $J_{H,P}$ 13 Hz); 7.3 - 7.6 (3H, m, m-, p-aryl H); 8.12 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 7 Hz); 9.30 (1H, broad s, NH). IR (Nujol): 1244, 1276 cm^{-1} (sh, str, $\nu_{P=O}$); 1682 (sh, str, $\nu_{C=O}$). IR (0.1% CCl_4 soln.): 1235, 1274 cm^{-1} (sh, str, $\nu_{P=O}$); 1683 (sh, str, $\nu_{C=O}$). Anal. calc. for $C_9H_{12}NO_4P$: C, 47.17; H, 5.28; N, 6.11%. Found: C, 47.05; H, 5.20; N, 6.05%.

R = Et (1b): The yellow oil formed by acidification is extracted with 20 cm^3 benzene, the extract dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure leaving a pale yellow solid. 47% yield, m.p. 71 - 73°C (pet. ether (60 - 80°C)). ^1H NMR ($CDCl_3$): δ 1.40 (6H, t, β-CH_3); 4.31 (4H, quintet, α-CH_2, $J_{H,H} = J_{H,P}$ 7 Hz); 7.3 - 7.6 (3H, m, m-, p-aryl H); 8.16 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 7 Hz). Anal. calc. for $C_{11}H_{16}NO_4P$: C, 51.36; H, 6.27; N, 5.45%. Found: C, 51.20; H, 6.30; N, 5.45%.

N-Acyl-N-methylphosphylamidates (1c-g).[100] To a stirred mixture of sodium sand (0.168 mol) and 150 cm^3 dry toluene, is added a solution of N-methylcarboxamide RCONHMe (0.168 mol; R = Me, Ph) in 20 cm^3 dry toluene dropwise over 30 min. The mixture is heated under reflux under anhydrous conditions until all the Na has disappeared, leaving a suspension of the salt. To the cooled suspension, is added dropwise with stirring, a solution of Z_2POCl (0.168 mol; Z = MeO, EtO, Et, $\sim CH_2O$) in dry toluene at a temperature of 5 - 10°C for substrates (1c-1f) and at 30 - 35°C for substrate (1g). The mixture is allowed to stir at room temperature for 16 - 18 h, filtered and the filtrate evaporated under reduced pressure leaving the crude product.

Z = MeO; R = Me (1c): The crude product is chromatographed, eluting with 20% ethyl acetate in chloroform to remove the MeCONHMe and then further purified by distillation:

Fraction 1: N-Acetyl-N-methyldimethylphosphoramidate (1c), 38% yield, b.p. 68 - 72°C (0.15 mm). ^1H NMR ($CDCl_3$): δ 2.39 (3H, s, $COCH_3$); 3.05 (3H, d, $PNCH_3$, $J_{H,P}$ 7.5 Hz); 3.83 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz). IR (0.1% CCl_4 soln.): 1294 cm^{-1} (str, sh, $\nu_{P=O}$); 1697 (str, sh, $\nu_{C=O}$). Anal. calc. for $C_5H_{12}NO_4P$: C, 33.15; H, 6.67; N, 7.73%. Found: C, 33.10; H, 6.72; N, 7.44%.

Fraction 2: Tetramethylpyrophosphate, b.p. 98 - 100°C (0.15 mm) (lit.[225b] b.p. 106 - 108°C (0.3 mm)). ^1H NMR ($CDCl_3$): δ 3.91 (d, $POCH_3$, $J_{H,P}$ 11 Hz). MS: m/e 234 (M^+). Anal. calc. for $C_4H_{12}O_7P$: C, 20.52; H, 5.17%. Found: C, 20.40; H, 5.05%.

Z = EtO; R = Me (1d): The crude product is chromatographed eluting with 20% ethyl acetate in chloroform to remove the MeCONHMe and further purified by distillation:

Fraction 1: N-Acetyl N-methyldiethylphosphoramidate (1d), 34% yield, b.p. 76 - 79°C (0.02 mm). ^1H NMR ($CDCl_3$): δ 1.38 (6H, t, β-CH_3, $J_{H,H}$ 7 Hz);

2.39 (3H, s, $COCH_3$); 3.04 (3H, d, $PNCH_3$, $J_{H,P}$ 7.5 Hz); 4.17 (4H, m, α-CH_2). IR (0.1% CCl_4 soln.): 1295 cm^{-1} (str, sh, $\nu_{P=O}$); 1697 (str, sh, $\nu_{C=O}$). Anal. calc. for $C_7H_{16}NO_4P$: C, 40.19; H, 7.71; N, 6.70%. Found: C, 39.75; H, 7.70; N, 6.55%.

Fraction 2: Tetraethylpyrophosphate, b.p. 110 - 111°C (0.05 mm) (lit.[225a] b.p. 138°C (1 mm)). ^1H NMR ($CDCl_3$): δ 1.39 (12H, t, β-CH_3, $J_{H,H}$ 7 Hz); 4.27 (8H, m, α-CH_2). MS: m/e 290 (M^+). Anal. calc. for $C_8H_{20}O_7P_2$: C, 33.11; H, 6.95%. Found: C, 33.25; H, 7.00%.

Z = EtO, R = Ph (1e): The crude product is chromatographed eluting with 20% ethyl acetate in chloroform to remove PhCONHMe and $[(EtO)_2PO]_2O$. Distillation is an ineffectual means of purification, owing to the similarity in the boiling points of (1e) and tetraethylpyrophosphate. 30% yield. ^1H NMR ($CDCl_3$): δ 1.22 (6H, t, β-CH_3, $J_{H,H}$ 7 Hz); 3.15 (3H, d, $PNCH_3$, $J_{H,P}$ 8 Hz); 4.03 (4H, m, α-CH_2); 7.3 - 7.6 (5H, m, aryl H). IR (5% CCl_4 soln.): 1268 cm^{-1} (med, sh), 1302 (str, sh, $\nu_{P=O}$); 1676 (str, sh, $\nu_{C=O}$). Anal. calc. for $C_{12}H_{18}NO_4P$: C, 53.13; H, 6.69; N, 5.16%. Found: C, 53.06; H, 6.62; N, 5.02%.

Z = Et, R = Me (1f): The crude product is purified by column chromatography eluting with 20% acetone in chloroform. 75% yield. ^1H NMR ($CDCl_3$): δ 1.11 (6H, d of t, CH_3, $J_{H,H}$ 8 Hz, $J_{H,P}$ 18 Hz); 1.9 - 2.2 (4H, m, CH_2); 2.25 (3H, s, $COCH_3$); 3.16 (3H, d, $PNCH_3$, $J_{H,P}$ 6.5 Hz). IR (0.1% CCl_4 soln.): 1195 cm^{-1} (str, sh, $\nu_{P=O}$); 1668 cm^{-1} (str, sh, $\nu_{C=O}$). Anal. calc. for $C_7H_{16}NO_2P$: C, 47.45; H, 9.10; N, 7.91%. Found: C, 47.30; H, 9.05; N, 7.75%.

Z_2 = ; R = Me (1g): The crude product is purified by column chromatography eluting with 33% acetone in chloroform, leaving an extremely hygroscopic oil which crystallises on standing. 72% yield, m.p. 56 - 58°C

(pet. ether (80 - 100°C)/acetone, 4:1). ^{1}H NMR ($CDCl_3$): δ 2.29 (3H, s, $COCH_3$); 3.23 (3H, d, $PNCH_3$, $J_{H,P}$ 9.0 Hz); 4.4 - 4.8 (4H, m, ring protons). IR (0.2% CCl_4 soln.): 1311 cm^{-1} (str, sh, $\nu_{P=O}$); 1695 (str, sh, $\nu_{C=O}$). Anal. calc. for $C_5H_{10}NO_4P$: C, 33.53; H, 5.63; N, 7.82%. Found: C, 33.70; H, 5.60; N, 7.65%.

9.4 MISCELLANEOUS REACTIONS

9.4.1 REACTIONS DISCUSSED IN CHAPTER 2.2

1. Reaction of $(EtO)_2PONNaMe$ with PhCOCl.

A solution of $(EtO)_2PONHMe$ (4 mmol) in 5 cm^3 dry benzene is added dropwise to a stirred suspension of NaH (4 mmol) in 15 cm^3 dry benzene and the mixture stirred at room temperature for 3 h. To the gelatinous suspension is added a solution of freshly distilled PhCOCl (4 mmol) in 5 cm^3 benzene. The mixture is heated under reflux (20 h), cooled and washed with water (2 x 5 cm^3). The benzene solution is dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure, yielding a dark yellow oil. TLC ($CHCl_3$ developing solvent) indicated the presence of three products of R_f values 0.9, 0.8 and 0.1 respectively; the mixture was separated into its components by column chromatography, eluting with $CHCl_3$.

Fraction 1: Ethyl benzoate (2.3). ^{1}H NMR ($CDCl_3$): δ 1.39 (3H, t, CH_3, $J_{H,H}$ 6 Hz); 4.38 (2H, q, CH_2); 7.2 - 7.6 (3H, m, m-, p-aryl H); 8.05 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 8 Hz). MS: m/e 150 (M^+).

Fraction 2: N-Methyldibenzimide (2.5), m.p. 96 - 97°C (pet. ether/acetone, 4:1). ^{1}H NMR ($CDCl_3$): δ 3.50 (3H, s, NCH_3); 7.1 - 7.3 (3H, m, m-, p-aryl H); 7.50 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 8 Hz). IR (10% CCl_4): 1659 cm^{-1} (str, sh, $\nu_{C=O}$). MS: m/e 239 (M^+). Anal. calc. for $C_{15}H_{13}NO_2$: C, 75.29; H, 5.50; N, 5.85%. Found: C, 74.80; H, 5.48; N, 5.85%.

Fraction 3: N-Methylbenzamide (2.4) (identified by comparison with genuine sample).

2. Reaction of $(EtO)_2PONNaMe$ with PhCOCl in the presence of a phase transfer catalyst.

To a stirred mixture of the sodium salt (12 mmol) prepared as above and TBAB (8 mol %) in 20 cm^3 dry toluene, is added a solution of PhCOCl (12 mmol) in 5 cm^3 toluene dropwise over 30 min. The addition reaction is exothermic and is accompanied by the formation of a white foam. The mixture is heated under reflux under anhydrous conditions for 15 h, filtered and evaporated under reduced pressure leaving a dark yellow oil. The product mixture was separated into its components by column chromatography, eluting with $CHCl_3$.

Fraction 1: Ethyl benzoate (2.3).

Fraction 2: N-Methyldibenzimide (2.5).

Fraction 3: N-Benzoyl-N,N'-dimethylbenzamidine (2.6), m.p. 114 - 116°C. ^1H NMR ($CDCl_3$): δ 3.15 (3H, s, NCH_3); 3.25 (3H, s, NCH_3); 7.2 - 7.8 (10H, m, aryl H). IR (5% CCl_4): 1658 cm^{-1} (str, sh, $\nu_{C=O}$); 1637 (med, sh, $\nu_{C=N}$). MS: m/e 252 (M^+). Anal. calc. for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.11%. Found: C, 75.70; H, 6.30; N, 10.45%.

Fraction 4: N-Methylbenzamide (2.4).

3. Selected reactions of $Z_2P(O)NHR$ with isopropenyl acetate in the presence of an acid catalyst.

(1) Brönsted acid catalyst

In a typical experiment, the amidate Z_2PONHR is heated with an excess of IPA in toluene in the presence of a catalytic amount of either 96% H_2SO_4 or anhydrous p-TSA (8 - 10 mol %). The mixture is heated under reflux until all the amidate has reacted and the product mixture obtained by removal of all volatile materials is subsequently subjected to column chromatography. The percentage composition of the product mixture is given in brackets.

Z = MeO, R = Me (H_2SO_4 catalyst): The product mixture obtained after 23 h under reflux was separated by column chromatography eluting with 20% ethyl acetate in chloroform.

Fraction 1: N-Methyldiacetimide (2.14a) (65%).

Fraction 2: (1c) (15%).

Fraction 3: N-Methylacetamide (2.13a) (20%).

Z = EtO, R = Me (H_2SO_4 catalyst): The product mixture obtained after 18 h under reflux was chromatographed, eluting with 20% ethyl acetate in chloroform.

Fraction 1: (2.14a) (65%).

Fraction 2: (1d) (35%).

Z = Et, R = Me (H_2SO_4 catalyst): The product mixture obtained after 23 h under reflux was chromatographed eluting with 20% ethyl acetate in chloroform.

Fraction 1: (2.14a) (10%).

Fraction 2: Unreacted N-methyldiethylphosphinamide (2.1c) (35%).

Fraction 3: (2.13a) (55%).

Z = MeO, R = Ph (p-TSA catalyst): The product mixture obtained after 22 h under reflux was chromatographed, eluting with 20% acetone in chloroform.

Fraction 1: N-Phenyldiacetimide, (2.14b) (60%). ^{1}H NMR ($CDCl_3$): δ 2.27 (6H, s, $COCH_3$); 7.1 - 7.5 (5H, m, aryl H). MS: m/e 177 (M^+), 149 (M-CO), 135 ($M-CH_2CO$); 43 ($MeCO^+$). Anal. calc. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.91%. Found: C, 67.55; H, 6.30; N, 7.70%.

Fraction 2: Acetanilide, (2.13b) (10%). ^{1}H NMR: δ 2.18 (3H, s, $COCH_3$); 7.10 (1H, broad s, NH); 7.2 - 7.4 (5H, m, aryl H). MS: m/e 135 (M^+). Anal. calc. for C_8H_9NO: C, 71.09; H, 6.71; N, 10.37%. Found: C, 70.55; H, 6.60; N, 10.45%.

Fraction 3: Unreacted N-phenyl dimethylphosphoramidate (2.1d) (30%).

(2) Lewis acid catalyst

The amidate $(MeO)_2PONHMe$ (2.1b) is heated under reflux with an excess of IPA in toluene in the presence of 80 mol % $BF_3.OEt_2$ for a period of 24 h. After removal of all volatile materials, the remaining black oil is subjected to column chromatography, eluting with 10% ethyl acetate in chloroform. The only product thus isolated was found to be a 1:3 mixture of N-methyldiacetimide (2.14a) and the boron difluoride complex (2.15). The latter was identified by repeating the above reaction in the absence of the amidate (2.1b) and purifying the resulting product by column chromatography, eluting with 20% ethyl acetate in chloroform. The Fries rearrangement product (2.15) thus obtained has the following spectral characteristics: ^1H NMR ($CDCl_3$): δ 2.31 (6H, s, $COCH_3$); 6.00 (1H, s, vinyl H). MS: m/e 148, 147 (M^+); 133, 132 ($M-CH_3^\cdot$); 129, 128 ($M-F^\cdot$); 83 ($M-OBF_2^\cdot$); 43 ($MeCO^+$).

9.4.2 REACTIONS DISCUSSED IN CHAPTER 6.[145]

1. Ethylation of (6.5) with triethyloxonium tetrafluoroborate.

(1) A solution of (1a) (10 mmol) in 50 cm^3 dry benzene is added dropwise to a stirred suspension of NaH (10 mmol) in 20 cm^3 benzene, forming a suspension of the sodium salt (6.5). The benzene is removed under reduced pressure leaving a white solid. ^1H NMR (d^6-DMSO): δ 3.55 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 7.4 - 7.5 (3H, m, m-, p-aryl H); 8.07 (2H, d of d, o-aryl H). IR (5% CCl_4 soln.): 1205 cm^{-1} (med, sh); 1370 (str, sh); 1550 (str, sh); 1595 (med, sh).

(2) To a stirred suspension of (6.5) (10 mmol) in 50 cm^3 dry dichloromethane, is added a solution of $Et_3O^+BF_4^-$ (10 mmol) in 10 cm^3 dichloromethane,

maintaining the temperature at 10 - 15°C. The mixture is stirred for a fixed length of time (5 - 20 h) and washed with water (25 cm^3). The solution is dried over anhydrous $MgSO_4$, filtered and the solvent evaporated under reduced pressure, leaving a yellow oil (71% yield). TLC (10% acetone in chloroform developing solvent) revealed two products of R_f values 0.40 and 0.56 respectively. The mixture obtained after a reaction time of 5 h was separated into its two components, eluting with 10% acetone in chloroform.

Fraction 1: N-Benzoyl-ethyldimethylphosphorimidate, (6.6). ^1H NMR ($CDCl_3$): δ 1.39 (3H, t, β-CH_3, $J_{H,H}$ 7 Hz); 3.92 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 4.30 (2H, quintet, α-CH_2, $J_{H,P} = J_{H,H}$ 7 Hz); 7.2 - 7.5 (3H, m, m-, p-aryl H); 8.18 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 8 Hz). IR (5% CCl_4 soln.): 1187 cm^{-1} (med, sh, δ_{CH_3} of $POCH_3$); 1347 (str, sh, $\nu_{P=N}$); 1611 (str, sh, $\nu_{C=O}$ with shoulder at 1624).

Fraction 2: (E)-N-Dimethylphosphoryl-O-ethylbenzimidate, (6.7a). ^1H NMR ($CDCl_3$): δ 1.42 (3H, t, CH_3, $J_{H,H}$ 7.5 Hz); 3.67 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 4.42 (2H, q, CH_2); 7.4 - 7.5 (3H, m, m-, p-aryl H); 7.92 (2H, d of d, o-aryl H, J_{meta} 2 Hz, J_{ortho} 8 Hz). ^{13}C NMR ($CDCl_3$, Hz downfield from TMS): 14.2 (s, CH_3 of O-Et group); 53.2 (d, OCH_3, $J_{C,P}$ 7.0 Hz); 64.0 (s, CH_2 of O-Et group); 125 - 135 (m, aromatic C and imidate C). IR (5% CCl_4 soln.): 1187 cm^{-1} (med, sh, δ_{CH_3} of $POCH_3$); 1271 (str, sh, $\nu_{P=O}$); 1657 (str. sh, $\nu_{C=N}$).

2. Ethylation of (6.5) with ethyl iodide in the presence of a phase transfer catalyst.

To a mixture of the sodium salt (6.5) (20 mmol, prepared as above) and TBAB (5 mol %) in 100 cm^3 dry benzene, is added a ten-fold excess of EtI. The mixture is heated under reflux with stirring for 21 h; the supernatant benzene solution is decanted and the white solid residue washed with 20 cm^3 benzene. The benzene is removed from the solution under reduced pressure

leaving the crude product (58% yield). The product is dissolved in 20 cm^3 chloroform, washed with water (2 x 5 cm^3), dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure, leaving a clear yellow oil which is subjected to column chromatography, eluting with 33% ethyl acetate in dichloromethane.

Fraction 1: The product has the same spectral characteristics as (6.7a) above.

Fraction 2: (Z)-N-Dimethylphosphoryl-O-ethylbenzimidate, (6.7b). ^1H NMR ($CDCl_3$): δ 1.42 (3H, t, CH_3, $J_{H,H}$ 7.5 Hz); 3.48 (6H, d, $POCH_3$, $J_{H,P}$ 11 Hz); 4.16 (2H, q, CH_2); 7.1 - 7.3 (5H, m, aryl H). ^{13}C NMR ($CDCl_3$, Hz downfield from TMS): 14.0 (s, CH_3 of O-Et group); 44.2 (s, CH_2 of O-Et group); 53.2 (d, OCH_3, $J_{C,P}$ 7.0 Hz); 125 - 135 (m, aromatic C, imidate C). IR (5% CCl_4 soln.): 1187 cm^{-1} (med, sh, δ_{CH_3} of $POCH_3$); 1268 (str, sh, $\nu_{P=O}$); 1654 (str, sh, $\nu_{C=N}$).

9.5 SOLVOLYSIS STUDIES

9.5.1 ALCOHOLYSIS

The stock solutions for acidic alcoholysis were prepared by passing dry hydrogen chloride into anhydrous alcohol, immediately standardising by titration and diluting appropriately with the same alcohol.

Kinetics

1. Neutral alcoholysis: The composition of a solution of substrate (0.15 mL), internal standard (0.05 mL; dimethyl ethylphosphate for methanolysis and trimethylphosphate for ethanolysis reactions) and anhydrous alcohol (5 mL) maintained at 25°C, was periodically analysed by GC by direct injection onto the column and concentrations (relative to the internal standard) measured according to peak integration. Pseudo first order rate

constants (k_ψ) obtained by following substrate disappearance and product appearance were identical; all kinetic runs were duplicated and k_ψ values found to be reproducible to a range of 2% of the average value.

2. Acidic alcoholysis: The reaction mixture consisting of substrate, internal standard and acidic alcohol (quantities and standards as above) was divided into ten equal portions, all maintained at 25°C. The portions were quenched at various times (the reactions were followed to approximately 85% completion) by neutralisation to pH 7 with oven-dried K_2CO_3 and immediately analysed by GC as above. Pseudo first order rate constants ($k_{\psi(P-N)}$, $k_{\psi(N-C)}$) were determined by both product appearance and substrate disappearance and final product ratio, and were found to be identical in all cases. All kinetic runs were made in duplicate using the same stock solution, all kinetic plots were found to be linear ($r > 0.999$) and rate constants calculated from duplicate runs were found to be reproducible to a range of 3% of the average value of the two runs.

9.5.2 HYDROLYSIS

Aqueous acidic solutions were prepared by diluting the concentrated D_2SO_4 with D_2O and standardised in the usual way. Kinetic runs were kept in a Haake thermostat, maintained at 25 ± 0.5°C.

Product determination

The substrate was dissolved in the acidic solution and the reaction monitored by recording its ^1H NMR spectrum. After reaction completion, the cleavage products were identified by spiking with authentic samples of N-methylacetamide, methylammonium chloride and sodium acetate. The following signals were used to identify reaction products and follow reaction kinetics:

entire acidity range, as was the rate of hydrolysis of the imide (7.9a) between 25 and 80% D_2SO_4.

pK determinations

Ionisation ratios which are relatively free of errors due to medium effects can be obtained from NMR spectra using the relationship:

$$I = [BH^+]/[B] = (\Delta-\Delta_B)/(\Delta_{BH^+}-\Delta)$$

where Δ_B is the chemical shift difference between a selected signal of the free base and an internal or external reference, Δ_{BH^+} is the chemical shift difference between a selected signal of the conjugate acid and the reference and Δ is the measured chemical shift difference in a given acidic medium. The rapid hydrolysis of imide (7.9a) in the 25 - 80% D_2SO_4 range precluded the measurement of ionisation ratios of this substrate. The acetyl singlet chemical shifts of substrate (1d) and (7.5a) were found to be the most sensitive to changing acidity and were thus used to measure Δ. The central peak of the β-CH_3 triplet of the OEt group was used as the internal reference for Δ determinations of (1d):

$$\Delta_{(1d)} = \delta_{\underline{CH_3}CO} - \delta_{OCH_2\underline{CH_3}}$$

Methylamine was used as an internal reference for Δ determinations of (7.5a):

$$\Delta_{(7.5a)} = \delta_{\underline{CH_3}CO} - \delta_{Me\overset{+}{N}D_3}$$

Measurements were made by injecting 0.01 mL substrate into an NMR tube containing 0.5 mL acid solution (and internal reference, where applicable) and immediately recording the spectrum over the appropriate range. The range of acid concentrations included *ca.* eight samples in the region $-1.0 \lesssim \log I \lesssim 1.0$ and solutions in which the substrate is unprotonated and fully protonated. Values of log I obtained were plotted according to the equation:

$$\log I = -mD_A + c$$

where D_A is the amide acidity function for D_2O - D_2SO_4. Högfeldt and Bigeleisen[196] have determined that the Hammett acidity functions H_o and D_o are identical in the range 0.6 M < $C_{L_2SO_4}$ < 12 M (L = H, D); extending this argument to the amide acidity function, for all solutions of concentration ≥ 6% D_2SO_4, $D_A = H_A$. Good straight lines were obtained ($r > 0.995$) from which the acidity functions at half-protonation ($D_A^{\frac{1}{2}}$) could be determined. Ionisation ratios of (1d) and (7.5a) calculated from shifts in the N-methyl absorptions yielded less satisfactory straight lines ($r \cong 0.97$).

9.6 CRYSTAL STRUCTURE DETERMINATION

Experimental details are described in Chapter 4. The observed and calculated structure factors (F_o, F_c) are listed below.

OBSERVED AND CALCULATED STRUCTURE FACTORS

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
2	0	0	97	-119	3	5	0	2	2	4	9	0	10	-9	2	14	0	13	13	2	20	0	5	-6
4	0	0	1	3	4	5	0	21	-19	5	9	0	4	-4	3	14	0	15	13	3	20	0	6	6
6	0	0	34	-36	5	5	0	10	-11	8	9	0	3	3	4	14	0	13	-14	4	20	0	11	12
8	0	0	11	12	6	5	0	2	-3	0	10	0	19	-22	5	14	0	12	-12	5	20	0	12	-11
2	1	0	2	1	7	5	0	5	5	1	10	0	6	7	6	14	0	4	3	1	21	0	5	-5
3	1	0	23	-25	0	6	0	64	60	2	10	0	33	32	7	14	0	2	3	2	21	0	11	11
5	1	0	10	-10	1	6	0	26	-22	3	10	0	2	-4	1	15	0	17	-16	3	21	0	10	10
6	1	0	5	6	2	6	0	45	-40	4	10	0	41	-40	2	15	0	13	13	4	21	0	6	6
7	1	0	25	26	3	6	0	34	-32	5	10	0	5	5	3	15	0	9	9	0	22	0	2	4
1	2	0	41	41	4	6	0	16	15	6	10	0	21	21	4	15	0	5	-5	1	22	0	11	-12
2	2	0	61	-64	5	6	0	19	18	7	10	0	7	-6	6	15	0	2	-1	2	22	0	9	-10
4	2	0	16	17	6	6	0	4	3	8	10	0	7	-7	0	16	0	33	-31	1	23	0	4	4
5	2	0	6	6	7	6	0	12	-12	1	11	0	10	10	1	16	0	6	-5	2	23	0	5	5
6	2	0	7	-7	8	6	0	4	-4	2	11	0	17	16	2	16	0	26	24	0	24	0	9	10
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-3	5	4	2	1	-4	8	4	9	-11	6	10	4	7	-7	-5	14	4	3	-3	1	18	4	10	10
-2	5	4	38	-36	-3	8	4	32	-32	-6	11	4	2	-2	-4	14	4	5	5	2	18	4	3	-3
-1	5	4	12	-10	-2	8	4	3	-2	-5	11	4	12	-12	-3	14	4	6	-6	3	18	4	7	-7
0	5	4	5	6	-1	8	4	21	19	-3	11	4	2	0	-2	14	4	3	-3	-2	19	4	7	7
2	5	4	16	-16	0	8	4	6	5	-2	11	4	10	-10	0	14	4	9	8	-1	19	4	3	3
4	5	4	29	30	1	8	4	21	-22	-1	11	4	18	-17	1	14	4	7	7	0	19	4	2	-2
6	5	4	9	-8	2	8	4	8	-8	0	11	4	20	19	2	14	4	12	-12	-5	0	5	2	-2
-7	6	4	8	-7	3	8	4	17	16	1	11	4	28	28	3	14	4	6	6	-3	0	5	7	6
-6	6	4	3	3	4	8	4	18	19	2	11	4	10	-9	4	14	4	5	5	-1	0	5	2	1
-5	6	4	4	4	5	8	4	5	-4	3	11	4	8	-8	5	14	4	6	-6	1	0	5	7	8
-4	6	4	2	-3	6	8	4	3	-3	4	11	4	5	4	-4	15	4	5	5	3	0	5	2	1
-3	6	4	4	5	-6	9	4	15	-15	5	11	4	4	4	-3	15	4	10	10	5	0	5	8	-10
-2	6	4	2	2	-5	9	4	9	-8	6	11	4	2	-2	-2	15	4	8	-8	-6	1	5	12	12
-1	6	4	14	13	-4	9	4	22	23	-5	12	4	5	5	-1	15	4	12	-12	-5	1	5	4	4
0	6	4	6	-6	-3	9	4	23	22	-4	12	4	15	15	0	15	4	5	-6	-4	1	5	18	-18
-3	1	5	11	-12	-5	4	5	8	7	1	7	5	19	-19	-1	11	5	8	8	1	16	5	3	4
-2	1	5	20	19	-4	4	5	2	3	2	7	5	7	-8	0	11	5	12	10	2	16	5	2	-3
-1	1	5	8	8	-3	4	5	4	-3	3	7	5	18	18	1	11	5	16	-16	-4	0	6	13	-13
0	1	5	14	-13	-2	4	5	6	-5	4	7	5	18	19	2	11	5	7	-7	-2	0	6	25	24
1	1	5	8	8	0	4	5	7	6	5	7	5	9	-9	3	11	5	4	4	0	0	6	4	-4
2	1	5	6	5	1	4	5	16	-17	-5	8	5	6	-6	4	11	5	3	3	2	0	6	16	17
3	1	5	8	8	2	4	5	7	-7	-4	8	5	2	-2	-3	12	5	4	4	4	0	6	23	-23
4	1	5	4	-4	3	4	5	15	15	-3	8	5	8	9	-2	12	5	2	1	-3	1	6	3	-4
5	1	5	9	-9	4	4	5	8	9	-2	8	5	3	1	-1	12	5	11	-12	-2	1	6	3	-2
6	1	5	3	4	-6	5	5	3	2	-1	8	5	3	-3	0	12	5	5	5	-1	1	6	11	-12
-6	2	5	6	7	-5	5	5	6	6	0	8	5	6	6	1	12	5	6	5	0	1	6	2	-2
-5	2	5	3	2	-4	5	5	2	-2	1	8	5	8	7	2	12	5	2	-3	1	1	6	8	8
-4	2	5	4	5	-3	5	5	20	-20	2	8	5	13	-13	3	12	5	6	-5	3	1	6	3	-1
-3	2	5	9	-10	-2	5	5	4	5	3	8	5	8	-8	-4	13	5	4	3	4	1	6	7	7
-2	2	5	16	-16	-1	5	5	19	19	4	8	5	8	8	-2	13	5	5	-4	-4	2	6	10	-11
0	2	5	6	-7	0	5	5	19	-20	5	8	5	2	1	-1	13	5	2	2	-3	2	6	2	3
1	2	5	3	-3	1	5	5	21	-21	-5	9	5	8	8	0	13	5	16	17	-2	2	6	7	7
2	2	5	4	4	2	5	5	5	5	-4	9	5	10	9	1	13	5	2	-2	-1	2	6	3	-4
3	2	5	5	5	3	5	5	20	21	-2	9	5	9	-8	2	13	5	11	-11	0	2	6	13	-13
4	2	5	3	3	4	5	5	12	13	-1	9	5	22	22	3	13	5	5	6	2	2	6	16	16
6	2	5	2	-2	5	5	5	9	-9	0	9	5	7	6	-3	14	5	6	6	3	2	6	8	9
-5	3	5	6	6	-4	6	5	7	7	1	9	5	26	-26	-2	14	5	3	2	4	2	6	8	-8
-4	3	5	8	-8	-3	6	5	24	25	2	9	5	12	-11	-1	14	5	11	-11	-4	3	6	5	5
-3	3	5	8	-7	-2	6	5	2	1	4	9	5	6	6	0	14	5	8	-8	-3	3	6	9	10
-2	3	5	29	27	-1	6	5	8	-7	5	9	5	4	-4	1	14	5	12	12	-2	3	6	2	-1
-1	3	5	11	11	0	6	5	7	8	-5	10	5	3	-2	3	14	5	4	-5	-1	3	6	6	-6
0	3	5	11	-11	1	6	5	2	-2	-4	10	5	9	-9	-2	15	5	6	-5	0	3	6	5	-6
1	3	5	6	-6	2	6	5	15	-15	-3	10	5	4	-4	-1	15	5	2	2	1	3	6	8	8
2	3	5	10	9	3	6	5	7	-7	-2	10	5	3	2	0	15	5	5	5	2	3	6	2	2
3	3	5	12	13	-5	7	5	4	4	0	10	5	13	14	1	15	5	5	5	3	3	6	4	-4
4	3	5	15	-15	-4	7	5	7	-7	1	10	5	6	7	2	15	5	10	-11	-4	4	6	9	-9
5	3	5	10	-11	-3	7	5	18	-18	-4	11	5	7	6	-2	16	5	3	3	-3	4	6	19	-19
6	3	5	3	3	-1	7	5	26	25	-3	11	5	3	-3	-1	16	5	3	3	-2	4	6	6	6
-6	4	5	3	-3	0	7	5	7	-7	-2	11	5	2	-1	0	16	5	2	-2	-1	4	6	9	9
0	4	6	16	-16	2	5	6	3	3	-2	7	6	4	3	1	8	6	13	-13	1	10	6	4	-5
1	4	6	5	-5	3	5	6	3	-3	-1	7	6	6	-6	2	8	6	3	-3	2	10	6	7	-7
2	4	6	10	9	4	5	6	6	-7	0	7	6	2	2	3	8	6	4	4	-2	11	6	2	2
3	4	6	19	19	-4	6	6	3	4	1	7	6	4	5	-2	9	6	2	-2	-1	11	6	2	-2
4	4	6	2	2	-3	6	6	9	-8	2	7	6	2	3	1	9	6	8	8	0	11	6	8	-9
-4	5	6	3	3	-2	6	6	4	4	3	7	6	4	3	2	9	6	2	-2	1	11	6	2	2
-3	5	6	6	6	-1	6	6	9	9	-3	8	6	2	2	3	9	6	2	-2	2	11	6	4	3
-2	5	6	5	5	0	6	6	6	-6	-2	8	6	6	-5	-2	10	6	8	-8	-1	12	6	2	3
-1	5	6	5	-4	1	6	6	18	-18	-1	8	6	8	8	-1	10	6	7	7	0	12	6	14	14
0	5	6	4	-5	3	6	6	11	11	0	8	6	3	-3	0	10	6	9	8	1	12	6	7	-8

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185. N-Methylation of $(MeO)_2P(O)NHPh$ results in a 30-fold increase in the rate of acid-catalysed P(O)-N hydrolysis in 3.55 M H_2SO_4.[65]

186. In 0.86 M HCl/EtOH, $k_{\psi(P-N)}^{298K}$ = 1.91 x 10^{-5} s^{-1}; the rate of P(O)-N ethanolysis of $(MeO)_2PONHMe$ is thus twice as fast as that of (1c) under the same conditions.

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207. Benzanilides have also been found to hydrolyse with log k_{ψ} linearly dependent upon log [acid].[208]

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209. The alternative r-parameter treatment is given by:[182,203]

$$\log k_{\psi} + \log \left[\frac{I+1}{I}\right] = r \log a_{H_2O} + \text{const.}$$

210. The r-value discrepancy arising from the use of the a_{D_2O} values for D_2O - D_2SO_4 mixtures obtained by Bus *et al.*[211] at 20°C for the interpretation of the hydrolyses recorded at 25°C in this work, would be relatively minor (< 5%).[182]

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212. The r-value for the hydrolysis of benzamide at 25°C is 3.14 in aqueous HCl[202] as opposed to 2.6 in aqueous H_2SO_4.[188]

213. Structure (7.18) is analogous to the proposed transition state in the acid-catalysed hydrolysis of aromatic amides.[191,203]

214. Analogous changes in the r-plot slopes of carboxylic esters, which are even less basic, have been found to occur at acidities as high as 85% H_2SO_4.[187]

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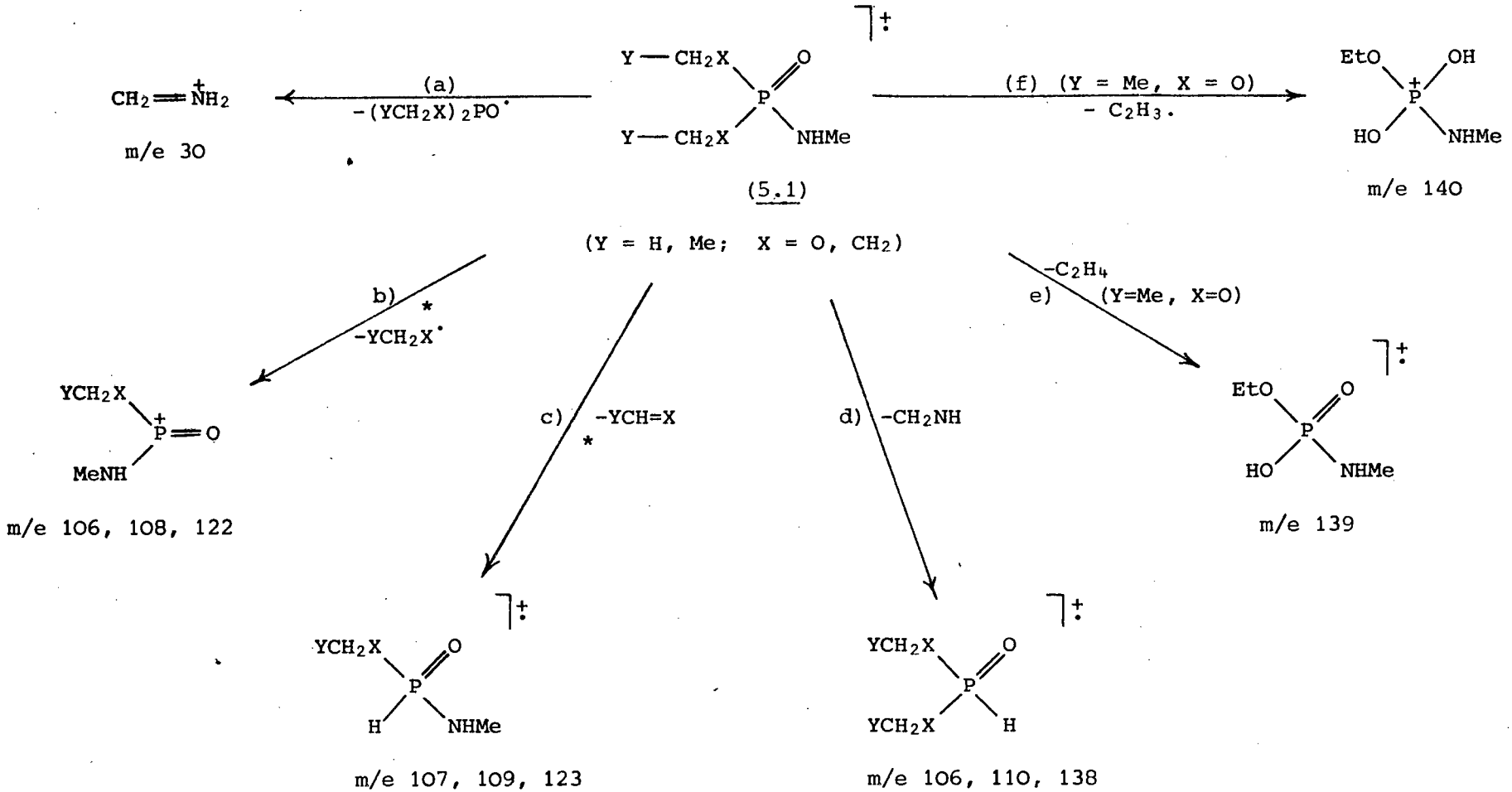
Scheme 5.1


(a)
-(YCH2X)2PO·
CH2=NH2
m/e 30
Y—CH2X
Y—CH2X
P
O
NHMe
(5.1)
(Y = H, Me; X = O, CH2)
(f) (Y = Me, X = O)
- C2H3·
EtO
OH
HO
NHMe
m/e 140
b)
-YCH2X·
YCH2X
MeNH
m/e 106, 108, 122
c)
-YCH=X
H
m/e 107, 109, 123
d)
-CH2NH
YCH2X
H
m/e 106, 110, 138
e)
-C2H4
(Y=Me, X=O)
EtO
HO
NHMe
m/e 139