THE ELECTROPHILICITY AND CHEMISTRY OF PHOSPHATE ESTERS

a thesis submitted to the

UNIVERSITY OF CAPE TOWN

in fulfilment of the requirements for

the degree of

DOCTOR OF PHILOSOPHY

by

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February 1986

to my parents

and my twin

CONTENTS

ABSTRACT (i)

ACKNOWLEDGEMENTS (iii)

CONFERENCE PROCEEDINGS (iv)

PUBLICATIONS (v)

GLOSSARY (vi)

CHAPTER 1 INTRODUCTION 1

CHAPTER 2 SYNTHESIS, REACTIVITY AND INTRAMOLECULAR EFFECTS OF PHOSPHORIC TRIESTERS 8

2.1 INTRODUCTION

2.2 SYNTHESIS OF BIS-(p-NITROPHENYL) PHOSPHATE ESTERS

2.2.1 SYNTHESIS OF THE PHOSPHORYLATING REAGENT: BIS-(p-NITROPHENYL) PHOSPHOROCHLORIDATE

2.2.2 SYNTHESIS OF SUBSTRATES

2.3 HYDROLYSIS OF THE BIS-(p-NITROPHENYL) PHOSPHATE ESTERS

2.3.1 INTRODUCTION

2.3.2 RESULTS

2.4 MASS SPECTROMETRY OF COMPOUNDS 2.1a-f

2.5 SYNTHESIS OF MIXED TRIESTERS OF PHOSPHORIC ACID

CHAPTER 3 PREPARATION OF SELECTED DIMETHYLARYL AND DIMETHYL(ARYLALKYL) PHOSPHATES 40

3.1 INTRODUCTION

3.2 SYNTHESIS OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE, A

3.2.1 SYNTHESIS INVOLVING TRIETHYLAMINE AS A BASE

3.2.2 SYNTHESIS INVOLVING 2,6-DIMETHYL PYRIDINE AS A BASE

3.2.3 SYNTHESIS IN THE ABSENCE OF AN EXTERNAL BASE

3.2.4 THE "ALKOXIDE ION METHOD"

3.3 SYNTHESIS OF DIMETHYL-[β-(2-PYRIDYLETHYL)] PHOSPHATE, B

3.4 SYNTHESIS OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE, C

3.5 SYNTHESIS OF DIMETHYL-(4-PYRIDYLMETHYL) PHOSPHATE, D

CHAPTER 4 REACTIVITY OF DIMETHYL (ARYLALKYL) PHOSPHATES 75

4.1 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE, A

4.1.1 INTRODUCTION

4.1.2 RESULTS

4.1.3 THE SYNTHESIS OF COMPOUNDS INVOLVED IN SCHEME 4.1, - 4.1, AI^+ and AI^-

4.1.4 THE SYNTHESIS OF (2-PYRIDYLMETHYL) ACETATE, E

4.1.5 O → N METHYL TRANSFER IN 2-PYRIDYLMETHYL DERIVATIVES

4.1.6 HYDROGEN/DEUTERIUM EXCHANGE

4.2 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-[β-(2-PYRIDYLETHYL] PHOSPHATE, B

4.2.1 INTRODUCTION

4.2.2 RESULTS

4.2.3 O → N METHYL TRANSFER IN β-(2-PYRIDYLETHYL) DERIVATIVES

4.3 A STUDY OF THE N-METHYLATING BEHAVIOUR OF DIMETHYL-(4-PYRIDYLMETHYL) PHOSPHATE, D

4.4 ALKYLATING PROPERTIES OF PHOSPHATE ESTERS.

OXYGEN → NITROGEN METHYL TRANSFER IN DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE

4.4.1 A ^1H NMR STUDY OF THE EFFECT OF CONCENTRATION ON THE RATE OF O → N METHYL TRANSFER - INTER- vs. INTRAMOLECULAR REACTION

4.4.2 INVESTIGATION OF THE O → N METHYL TRANSFER REACTION MECHANISM BY ^{13}C NMR SPECTROSCOPY

4.4.3 ^{31}P NMR SPECTROSCOPY AS A TOOL FOR INVESTIGATION OF O → N METHYL TRANSFER

CHAPTER 5 REACTIVITY OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE 151

5.1 INTRODUCTION

5.2 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE

5.3 THE SYNTHESIS OF COMPOUNDS INVOLVED IN SCHEME 5.1.

5.3.1 METHYL-[8-(N-METHYLQUINOLINIUM)] PHOSPHATE, 5.1

5.3.2a DIMETHYL-[8-(N-METHYLQUINOLINIUM)] PHOSPHATE TRIFLUOROMETHANESULFONATE, $\underline{CI}^{+}$

5.3.2b DIMETHYL-[8-(N METHYLQUINOLINIUM)] PHOSPHATE METHYLSULPHATE, $\underline{CI}^{+}$

5.3.3 THE MONO-SODIUM SALT OF 8-QUINOLYLMETHYL PHOSPHATE, $\underline{CI}^{-}$

5.3.4 8-HYDROXY-(N-METHYLQUINOLINIUM) IODIDE

5.4 A SEMI-QUANTITATIVE STUDY OF O→N METHYL TRANSFER IN QUINOLYL DERIVATIVES

5.4.1 INTRODUCTION

5.4.2 RESULTS AND DISCUSSION

5.4.3 SYNTHESIS OF 8-QUINOLYL ACETATE

CHAPTER 6 THE MOLECULAR AND CRYSTAL STRUCTURE OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE 185

6.1 INTRODUCTION

6.2 EXPERIMENTAL

6.3 SOLUTION AND REFINEMENT OF THE STRUCTURE

6.4 DISCUSSION

CHAPTER 7 MASS SPECTROMETRY OF DIMETHYLARYL, DIMETHYL-(ARYLALKYL) PHOSPHATES AND RELATED ACETATES 211

7.1 INTRODUCTION

7.2 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE, A

7.3 FRAGMENTATION BEHAVIOUR OF DIMETHYL-[β-(2-PYRIDYLETHYL)] PHOSPHATE, B

7.4 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE, C

7.5 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(4-PYRIDYLMETHYL) PHOSPHATE, D

7.6 FRAGMENTATION BEHAVIOUR OF (2-PYRIDYLMETHYL) ACETATE, [β-(2-PYRIDYLETHYL)] ACETATE AND 8-QUINOLYL ACETATE

7.6.1 2-PYRIDYLMETHYL ACETATE, E

7.6.2 [β-(2-PYRIDYLETHYL)] ACETATE, F

7.6.3 8-QUINOLYL ACETATE

CHAPTER 8 METHYL TRANSFER FROM TRIMETHYL PHOSPHATE TO PYRIDYL NITROGEN 249

8.1 INTRODUCTION

8.2 RESULTS

8.3 DISCUSSION

8.3.1 REACTIONS IN PURE SOLVENTS

8.3.2 REACTIONS IN MIXED SOLVENTS

8.4 CONCLUSION

CHAPTER 9 FRAGMENTATION OF β-ARYLETHYL PHOSPHATE ESTERS 279

9.1 INTRODUCTION

9.2 SYNTHESIS OF (β-ARYLETHYL)PHOSPHOROCHLORIDATES AND RELATED COMPOUNDS

9.3 FRAGMENTATION OF (β-ARYLETHYL)PHOSPHOROCHLORIDATES

9.4 ELECTRON IMPACT-INDUCED FRAGMENTATION OF (β-ARYLETHYL)PHOSPHOROCHLORIDATES

CHAPTER 10 CONCLUSION 315

CHAPTER 11 EXPERIMENTAL 319

11.1 GENERAL

11.2 REAGENTS

11.3 SUBSTRATES

11.4 BASE CATALYSED HYDROLYSIS

11.5 O→N METHYL TRANSFER

11.5.1 SEMI-QUANTITATIVE RESULTS

11.5.2 REACTION DISCUSSED IN CHAPTER 4.4

11.5.3 RATE MEASUREMENTS

11.6 CRYSTAL STRUCTURE DETERMINATION

11.7 ANCHIMERIC ASSISTANCE STUDIES

APPENDIX I - IV 348

REFERENCES AND NOTES 380

Abstract

A series of phosphate esters containing the p-nitrophenyl moiety as a leaving group were synthesised and their base catalysed hydrolysis and electron impact-induced fragmentations studied. Heterocyclic ester substituents were present in some of the substrates and in this sense they were considered as models for a nucleotide molecule containing both the "energy-rich" phosphate bond and the nitrogen heterocyclic ring. The relative reactivity of the phosphorus-p-nitrophenoxide bond was taken as a probe for nitrogen (pyridyl or quinolyl) participation in the substitution reaction. Although the heterocyclic derivatives show that the introduction of the nitrogen centre increases the rate of base-catalysed hydrolysis, the reactivity enhancement is not significant and results probably from polar effects rather than from intramolecular catalysis. A comparison of the mass spectra of the heterocyclic and carbocyclic analogues, reveal differences which are significant (in the pyridyl substrates) and dramatic (in the quinolyl substrate) with regard to the fragmentation involving the p-nitrophenoxy radical expulsion and formation of the corresponding phosphorylium ion.

Synthetic approaches towards dimethylaryl and dimethyl(arylalkyl) phosphates are discussed. Nucleophilic displacement at the methyl ester carbon, and in particular the oxygen → nitrogen methyl group transfer in these substrates occurs readily, complicating the synthetic procedures and lowering the stability of products. Dimethyl-(2-pyridylmethyl) phosphate isomerises in water to the zwitterionic N-methylpyridinium derivative *via* bimolecular methylation. The kinetics of the reaction were studied and no evidence for intramolecular methyl transfer was obtained.

The isomerisation of dimethyl-(quinolin-8-yl) phosphate in water also provides evidence for the bimolecular methylation. The crystal and molecular structure of dimethyl-(quinolin-8-yl) phosphate was determined and has revealed that the orientation of the CH_3 groups in the crystal provide no indication for the occurrence of methyl transfer in the solid state.

The dynamics of the prepared phosphate derivatives studied in solutions were also investigated by means of mass spectrometry. Fragmentation patterns and their relative contributions are presented and discussed.

The effect of solvent on the rates of the reaction between trimethyl phosphate and i) pyridine and ii) 4-(dimethylamino)-pyridine, was studied at 25 - 65°C using NMR techniques. The solvents used were D_2O, CD_3OD, CD_3CN and D_2O/CD_3OD and D_2O/CD_3CN mixtures. Water (D_2O) is the most effective medium for the methyl transfer reaction. We attribute this to the strong hydrogen bonding between water and the departing dimethyl phosphate anion in the transition state. Activation parameters obtained for the reactions in pure solvents confirmed our interpretation of the hydrogen bonding effect operating in the transition state.

Fragmentation of β-arylethyl phosphates has been investigated. A novel feature is exhibited by β-arylethyl phosphorochloridates. They easily decompose thermally yielding 1-chloro-2-arylethanes and/or arylethylenes presumably *via* concerted C-O and P-Cl bond fission involving a phenonium ion intermediate and expulsion of a metaphosphate species.

Acknowledgements

I wish to express my thanks to

Assoc. Prof. Tom A. Modro, my supervisor and friend, for his continual guidance and encouragement;

Bridgit Williamson, Dr. Klaus Koch, Noel Hendricks, Zayed Brown and Toby Hemsted for their helpful service;

Moira Armstrong, Dr. Diana Bond, Alfie le Roux and Afzal Dhansay, my colleagues and friends, for their contributions to this project;

Dr. Margaret Niven, for her assistance in structure determination;

Dr. Sunil Vather, for proof-reading this thesis;

My colleagues in the School of Chemical Sciences, for their friendship;

Patsy Alexander, for typing this thesis;

Beit Trust, the Council for Scientific and Industrial Research and the University of Cape Town for financial support.

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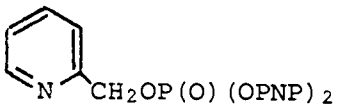
Glossary

SYMBOLS AND ABBREVIATIONS

DNA	Deoxyribonucleic acid
RNA	Ribonucleic acid
ATP	Adenosine triphosphate
ADP	Adenosine diphosphate
PNPO	p-nitrophenoxy
Nu	nucleophile
An	p-methoxyphenyl
TMP	trimethyl phosphate
DMP	dimethyl phosphate
4DMAP	4-(dimethylamino)-pyridine
H/D	hydrogen/deuterium
TLC	thin layer chromatography
M^+	molecular ion
m/e	mass to charge ratio
σ_I	inductive parameter
σ^*	Taft substituent constant

STRUCTURAL FORMULAE OF COMPOUNDS INVESTIGATED



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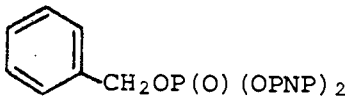

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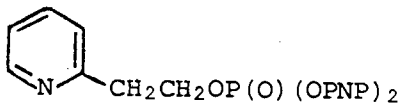

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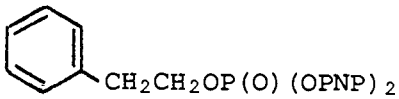

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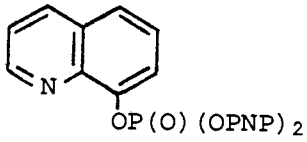

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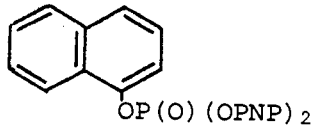

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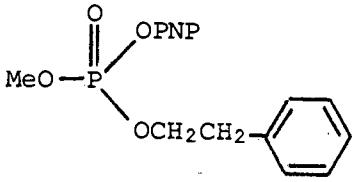

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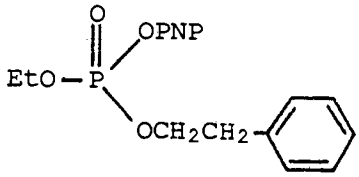

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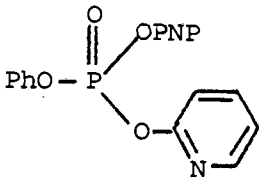

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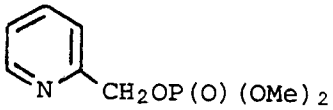

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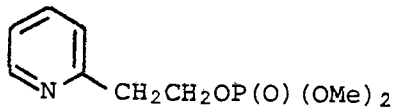

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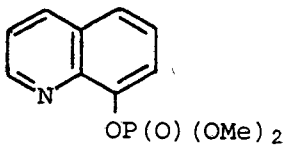

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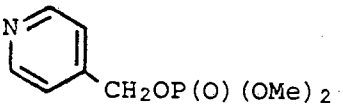

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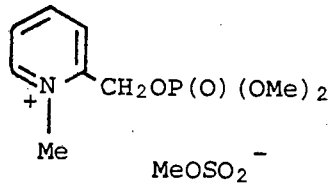

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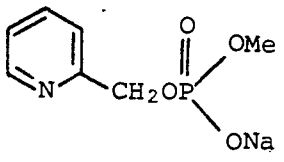

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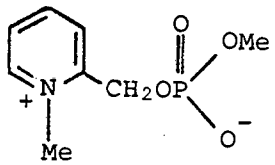

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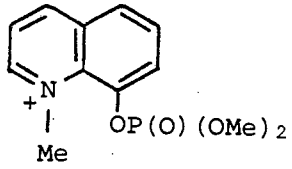

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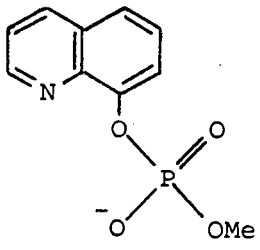

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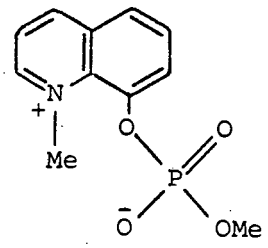

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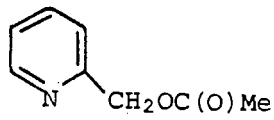

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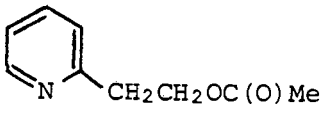

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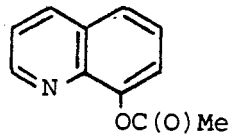

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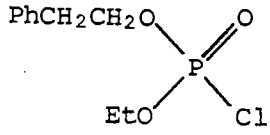

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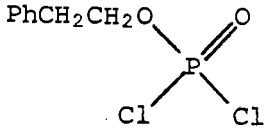

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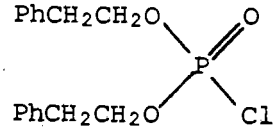

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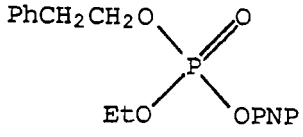

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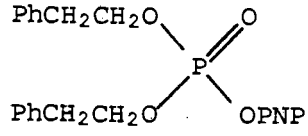

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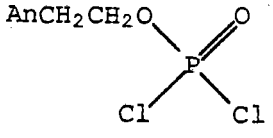
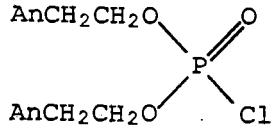
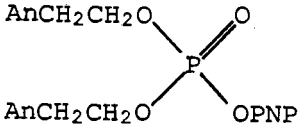


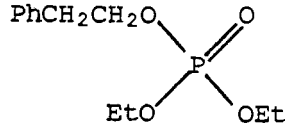
9.1f



9.1g



9.1h

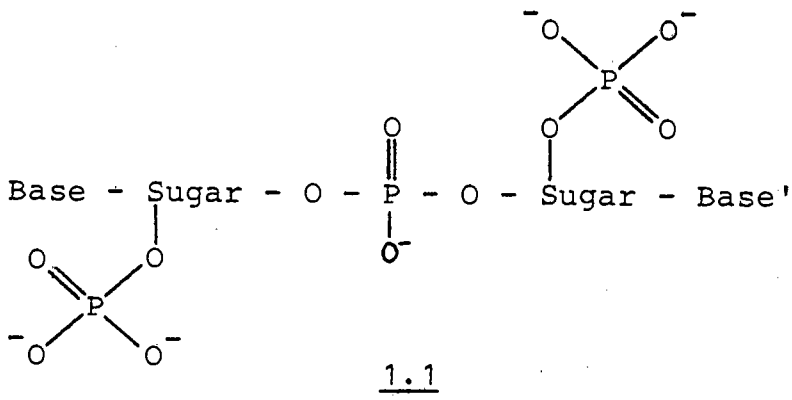


9.1i

Chapter 1

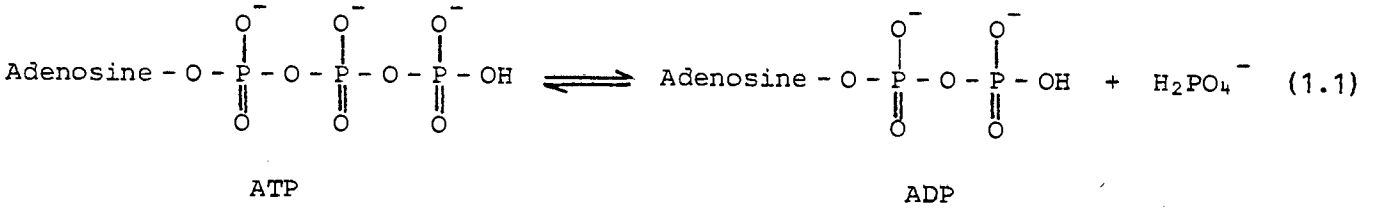
Introduction

Phosphates may be defined in the broadest sense as compounds derived from orthophosphoric acid, H_3PO_4. Many of the most essential chemicals in life processes are phosphate esters and these include the genetic substances DNA - the polymeric molecule whose function is to both store and pass on information, and RNA - the related polymer which helps in the passage of genetic information. The importance of phosphate in DNA and RNA macromolecules has been described.[1] It serves as an intergral part of the molecular "backbone" as well as the means by which the monomeric units are connected (see 1.1). In addition, the ionized PO_2^- moiety forms the



1.1

hydrophilic part of the system. Phosphate esters also play an essential part in photosynthesis, carbohydrate and lipid metabolism, the nitrogen cycle and numerous other biochemical reactions where they are the principle source of energy transfer. The reversible phosphate transfer between adenosine triphosphate (ATP) and adenosine diphosphate (ADP), eq. 1.1, is of fundamental importance in the energetics of biological systems.



(1.1)

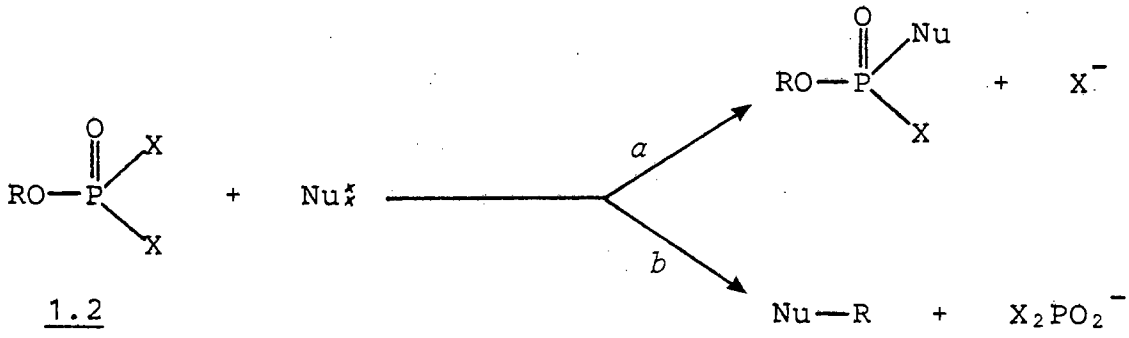
All the biological reactions involving formation and hydrolysis of these and other phosphate esters, and polyphosphates are effected by enzyme catalysis which is indispensable to achieve useful rates of reaction.

Because of the importance of such substances and processes as those just mentioned, nucleophilic cleavage, in particular the hydrolysis of phosphate esters, has received much fundamental study, in an attempt to understand the mechanism of the phosphorylation process.[2] The term "phosphorylation" is used in organophosphorus chemistry to cover the transfer of whole esterified groups such as $(RO)_2P(O)$ from one nucleophilic atom Y to another Z (eq. 1.2).

$$(RO)_2P(O)Y + Z^{\ddagger} \longrightarrow (RO)_2P(O)Z + Y^{\ddagger} \qquad (1.2)$$

As part of our research on the chemistry of phosphate esters, we have synthesized a number of compounds which we believe can serve as simple structural models for nucleotide and related systems. These involve a reactive phosphate derivative containing a good leaving group (e.g. p-nitrophenoxy, chlorine, etc.) and also an ester group (e.g. pyridyl or β-arylethyl) capable of nucleophilic contribution to the overall reactivity of the substrate. The hydrolysis of nitrophenyl phosphodiesters is catalyzed by pyridine-type buffers via a nucleophilic pathway involving a phosphopyridine intermediate,[3] so intramolecular catalysis by pyridine-like groups is not unfounded and is dependent on the intrinsic nucleophilicity

of the system as well as on steric, conformational and entropy factors. The systems we chose to study are also of a multi-centre nature and therefore offer an insight into the simultaneous interactions between a variety of functional groups. There are two electrophilic centres in a molecule of a phosphoric ester derivative 1.2, the phosphorus atom and the α-carbon atom of the ester group R. Nucleophilic attack at 1.2 can therefore lead to displacement at phosphorus (phosphorylation, pathway *a*) or to dealkylation (pathway *b*) with the phosphate anion as leaving group.

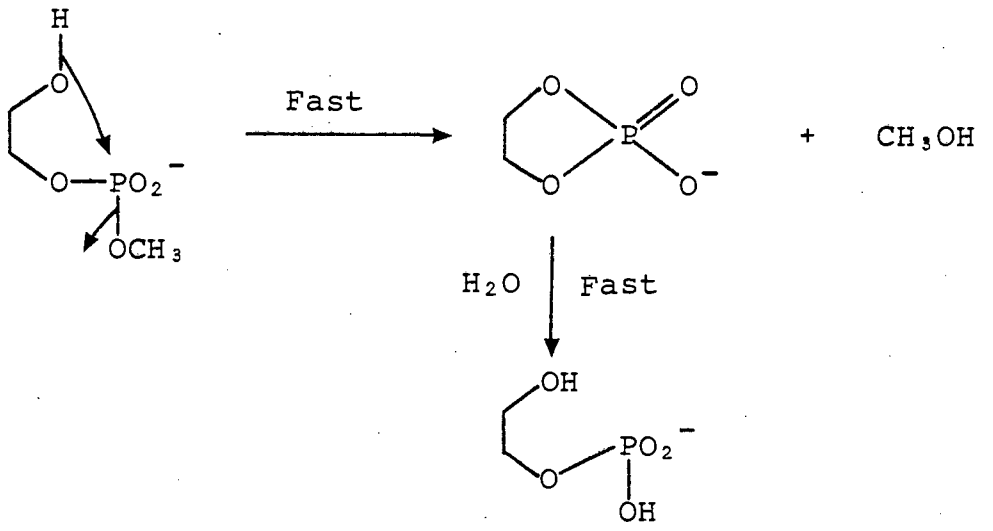


1.2 (1.3)

The growing interest in nucleophilic displacement at the carbon atom of phosphate esters stems from at least two sources. Firstly, alkylation of nucleotides by trialkyl phosphates[4] is related to studies on alkylated nucleosides which have been found in nucleic acids. Secondly, the "triester method" for the synthesis of oligonucleotides involves cleavage of the methyl phosphotriester intermediate by nitrogen[5] or sulphur[6] nucleophiles. Alkylating agents have been found to be detrimental to living systems. Trimethyl phosphate causes mutagenic and carcinogenic effects in male mice and Neurospora.[7] It has been suggested that the alkylation of nucleic acids, particularly DNA is a cause of mutagenic effects because alkylation results in modified nucleotides which are unable to perform normal biological functions.[4] In spite of this,

relatively little mechanistic work pertaining to reactions at the α-carbon of phosphate esters has been reported. For example, although phosphorylation reactions are susceptible to anchimeric assistance effects, as illustrated by the intramolecular catalysis responsible for the greater hydrolytic reactivity of 2-hydroxyethyl phosphates relative to esters with no hydroxy function in the β-position,[1] (scheme 1.1), no such similar study involving anchimeric assistance at the α-carbon with phosphate as leaving group has been investigated.

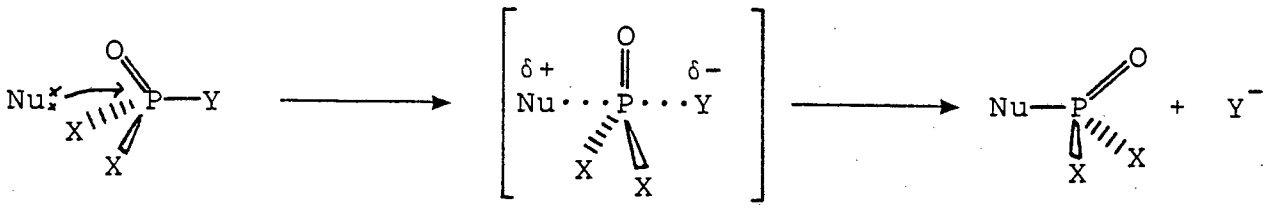
Scheme 1.1



Alkyl esters of phosphoric acid can act as alkylating agents with respect to a variety of nucleophiles.[8] The chemical potential of these systems is large, as a change both in the nucleophilic agent as well as in the leaving group structure (by modification of the groups at phosphorus), is conceivable. In phosphates containing both a nucleophilic centre and an electrophilic carbon in the phosphate ester group, alkyl transfer results in isomerisation and formation of the zwitterionic product. This reaction has been

employed[9] in the synthetic approach to phospholipid analogues. For example, the N-methylating properties of the methyl phosphate group have been demonstrated for phosphate esters derived from 2-(N,N-dimethylamino) ethanol. Although this isomerisation (transfer of the O-methyl group to the β-dimethylamino group in a phosphate triester) is believed[9] to be inter- not intramolecular, no evidence for the mechanism has been given. Manninen[10] claimed on the basis of "the effect of different concentrations", and "the appearance of the intermediate products" in the ^{1}H NMR spectra of the reaction mixture, that the methyl transfer is a bimolecular process. One of the objectives of this project is to investigate the mechanism of such an O→N methyl group transfer (intra- and/or intermolecular) in phosphate triesters. In addition, we intend to evaluate the medium effects on this transfer. Since the reaction from the point of view of the environment at phosphorus involves a change from a neutral triester to an ionic diester system, known to show highly hydrophilic properties,[1] the effect of water on the methyl group transfer is of particular interest.

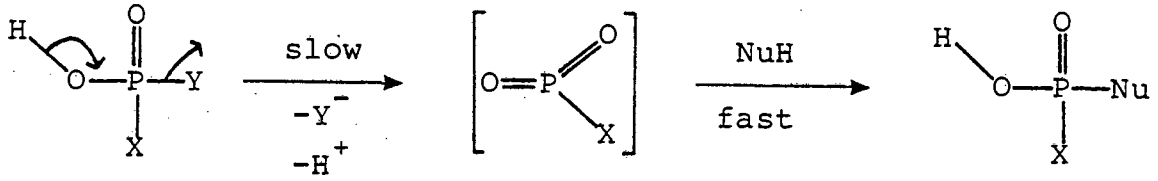
Generally, tetracoordinate phosphorus compounds react by electron pair mechanisms utilizing the electrophilicity of the phosphorus atom. Nucleophilic displacement at phosphorus can, as in carbon chemistry, follow two general mechanisms.[11] Firstly, the bimolecular mechanism is depicted in eq. 1.4 and structure 1.3 represents either the transition state or the pentavalent intermediate having a finite life time.



(1.4)

1.3

The other common mechanism for substitution at phosphorus can be considered analogous to S_N1 substitution at saturated carbon. This involves the unimolecular collapse of a substrate with the expulsion of the metaphosphate species 1.4 in which the coordination number at phosphorus has been reduced to three.



(1.5)

1.4

The "metaphosphate mechanism" is usually promoted by a negative charge in the precursor molecule. There have been no reports on the metaphosphate species arising from reaction at the α-carbon atom of a phosphate substrate. It is, however, conceivable that the C-O bond cleavage (pathway *b*, eq. 1.3) can, for substrates with a good leaving group present at phosphorus, involve fragmentation of the leaving group with formation of the metaphosphate derivative. This possibility is tested for phosphate derivatives containing an aromatic substituent in the β position of the ester alkyl chain.

Most of our reactivity studies relate to solutions or neat liquids. However, we intend to correlate the chemical behaviour of a selected

organic phosphate substrate in solution with its molecular parameters determined by X-ray diffraction. Also, whenever possible, we decided to parallel our studies by mass spectrometry. As mass spectral data on phosphate esters is scarce,[12] we hoped to characterize our substrates by this technique and so provide more general mass spectral information on organophosphorus compounds. Further, electron impact-induced fragmentations offer an insight into the chemical behaviour of a molecule under conditions free from any intermolecular effects or reactions.

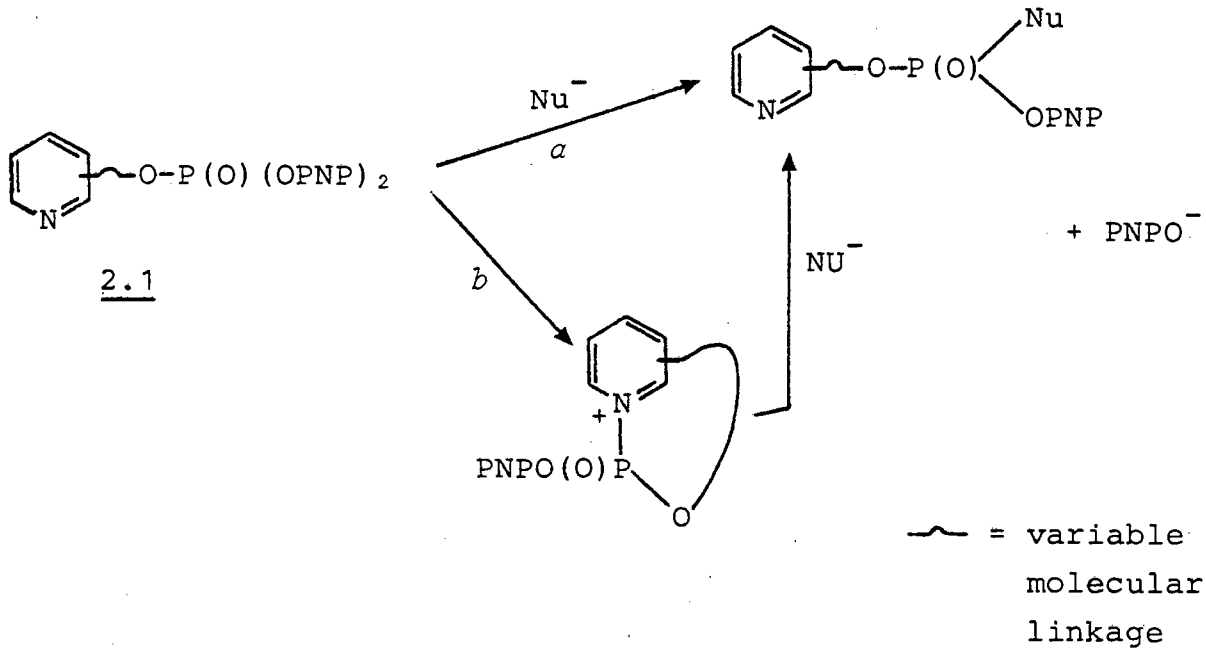
Chapter 2

Synthesis, Reactivity and Intramolecular Effects of Phosphoric Triesters

2.1 INTRODUCTION

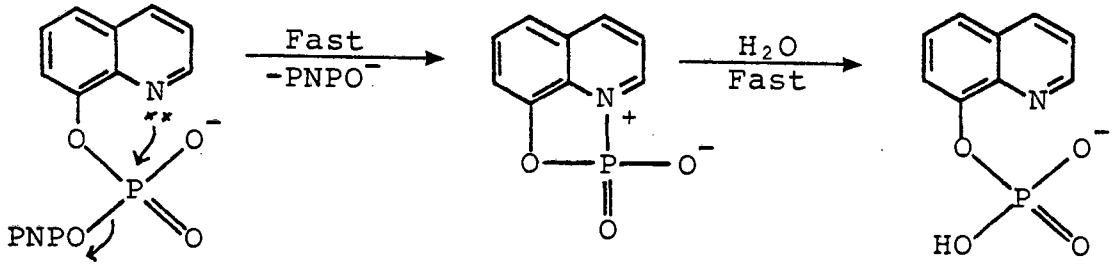
Phosphoric esters of the type 2.1 can be considered as simple models for biological phosphorylating molecules, eg. Adenosine Triphosphate (ATP): they have a good leaving group (p-nitrophenoxy, PNPO), an "energy rich" bond (P~OPNP) which models the anhydride bond in the ATP molecule and contain the tertiary nitrogen atom which can participate in the phosphorylation reaction. Nucleophilic displacement at substrates 2.1 can proceed either directly (pathway *a*, scheme 2.1) or via the mechanism involving intramolecular catalysis by nitrogen (pathway *b*, scheme 2.1).

Scheme 2.1



Intramolecular nucleophilic catalysis in the displacement of the phosphoryl substrate continues to be a subject for investigation[13] and recently Loran and Williams[14] described the hydrolysis of 4-nitrophenyl quinolin-8-yl phosphate. Intramolecular nucleophilic attack with expulsion of 4-nitrophenoxide giving a cyclic

intermediate (eq. 2.1) resulted in *ca.* a 350-fold rate increase for the hydrolysis of 2.2 relative to the reactivity of the 4-nitrophenyl phenyl phosphate.



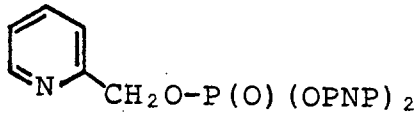
(2.1)

2.2

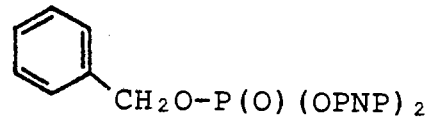
$PNPO^-$ = p-nitrophenoxide ion.

A number of compounds (2.1) have been synthesized and the preliminary results on their base-catalysed hydrolysis and electron impact-induced fragmentation has been obtained and compared with their phenyl analogues (phenyl instead of the pyridyl group in 2.1), for which no intramolecular catalysis is possible.

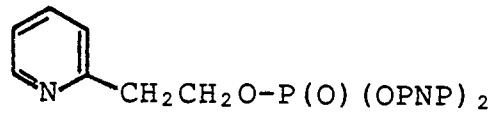
The first objective of this project was to synthesize and characterize three pairs of phosphate esters 2.1a-f and to compare their chemical behaviour.



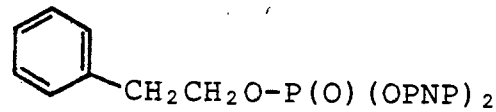
2.1a



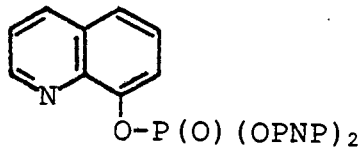
2.1b



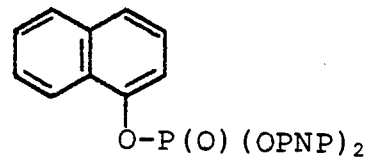
2.1c



2.1d

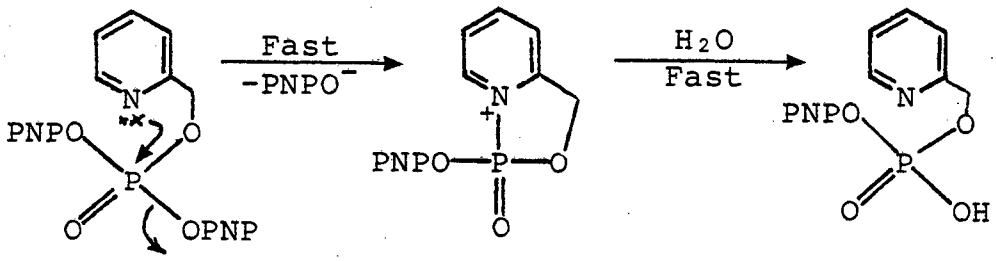


2.1e



2.1f

It is conceivable that the tertiary nitrogen atom in 2.1a can participate in the hydrolysis reaction (eq. 2.2) with formation of a cyclic intermediate 2.3 and expulsion of 4-nitrophenoxide.



(2.2)

2.3

For the derivative of β-(2-pyridyl)-ethanol (2.1c), the 6-membered analogue of 2.3 can be expected, while for the phosphate derived from 8-hydroxyquinoline, we suspect that intramolecular N→P interactions should be more favourable than in 2-pyridylmethanol and β-(2-pyridyl)-ethanol derivatives, because of the greater rigidity of the POCCN skeleton. No catalysis is possible of course, for

systems 2.1b, 2.1d and 2.1f, derived from the non-nitrogen alcohols, such as benzyl, 2-phenylethanol and 1-naphthol, respectively.

The following aspects of structure and reactivity for compounds 2.1a-f were investigated:-

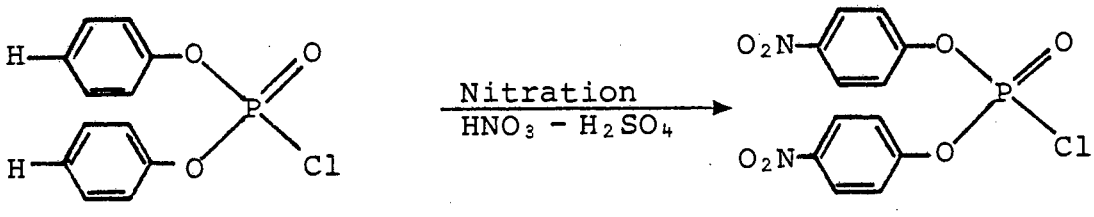
i) The kinetics of the base-catalysed hydrolysis. Here the reactivity of 2.1a-f towards basic hydrolysis was investigated from which the possibility of intramolecular nucleophilic catalysis of compounds 2.1a, 2.1c and 2.1e was deduced. The relative reactivity of the p-nitrophenyl phosphoric esters was determined by measuring (using UV spectrophotometry) rates of the release of p-nitrophenoxide ion in aqueous solutions.

ii) Electron impact-induced fragmentation patterns (mass spectrometry).

2.2 SYNTHESIS OF BIS-(p-NITROPHENYL) PHOSPHATE ESTERS

2.2.1 SYNTHESIS OF THE PHOSPHORYLATING REAGENT: BIS-(p-NITROPHENYL) PHOSPHOROCHLORIDATE.

The phosphorylating reagent was prepared by nitration of diphenyl phosphorochloridate as illustrated in eq. 2.3.[15]



(2.3)

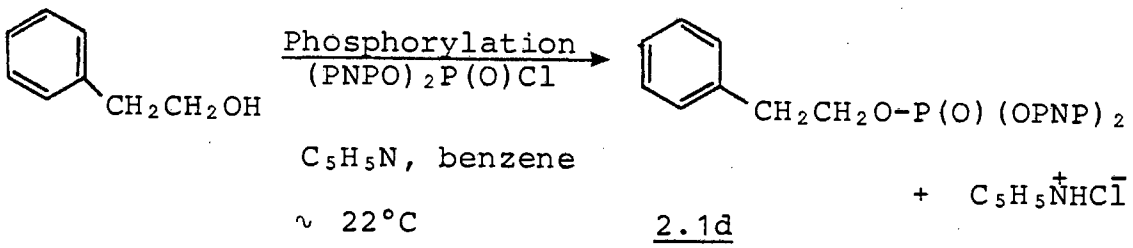
The bis-p-nitro derivative was easily obtained. There was good agreement between the experimental and theoretical composition of the nitrated product. ^{1}H NMR spectroscopy confirmed the identity of the pure product (see experimental section).

2.2.2 SYNTHESIS OF SUBSTRATES

The synthesis of 2.1a, 2.1b, 2.1e and 2.1f has been described elsewhere[16] and for reasons of brevity are not included here. However, the kinetic and mass spectral results are discussed.

SYNTHESIS OF BIS-(p-NITROPHENYL)(β-PHENYLETHYL) PHOSPHATE, 2.1d

The target phosphate ester was synthesized in one step as illustrated in eq. 2.4.

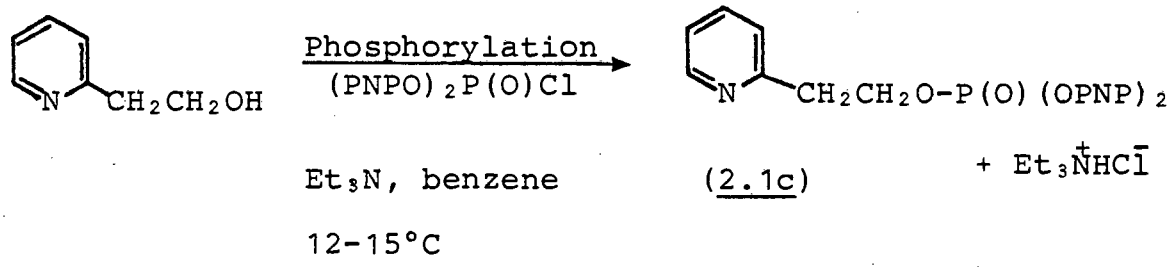


(2.4)

Esterification of the phosphorylating reagent with 2-phenylethanol was carried out using benzene as solvent and pyridine as the base to remove the HCl formed during the reaction. The reaction mixture was stirred at ambient temperature for 20 h. The precipitate of pyridinium chloride was removed by filtration and the crude product obtained by removing the solvent from the filtrate. The product was purified by column chromatography. There was good agreement between the experimental and theoretical composition of the phosphorylated product. The ^{1}H NMR spectrum of 2.1d (fig. 2.1) showed a distinct quartet and triplet characteristic of the P-OCH$_2$CH$_2$ grouping.

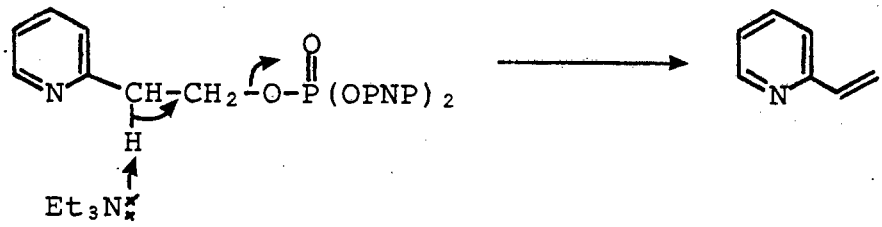
SYNTHESIS OF BIS-(p-NITROPHENYL)[β-(2-PYRIDYLETHYL)] PHOSPHATE, 2.1c

The target phosphate ester 2.1c was synthesized as illustrated in eq. 2.5.



(2.5)

Initial experiments showed that when a mixture of tetrahydrofuran (THF) and diethyl ether were used as the solvent (bis-(p-nitrophenyl) phosphorochloridate is poorly soluble in benzene) less satisfactory results were obtained. Although the ^{1}H NMR spectrum of the reaction product showed the formation of 2.1c, it also revealed the presence of 2-vinylpyridine, presumably formed by a base-catalysed elimination reaction (eq. 2.6).



(2.6)

The product 2.1c was finally prepared using benzene as the solvent. After filtering off triethylammonium chloride, the solvent could be removed at low temperature and no elimination was observed. Crude 2.1c was then recrystallized from benzene/petroleum ether yielding the pure product, the ^{1}H NMR spectrum (fig. 2.2) being in agreement with the expected structure. The downfield shift of the quartet ($\Delta\delta$0.17) and triplet ($\Delta\delta$0.13) for the P-O-CH_2- and P-OCH_2CH_2- protons

Figure 2.1 ^{1}H NMR spectrum of bis-(p-nitrophenyl)-(β-phenylethyl) phosphate, 2.1d

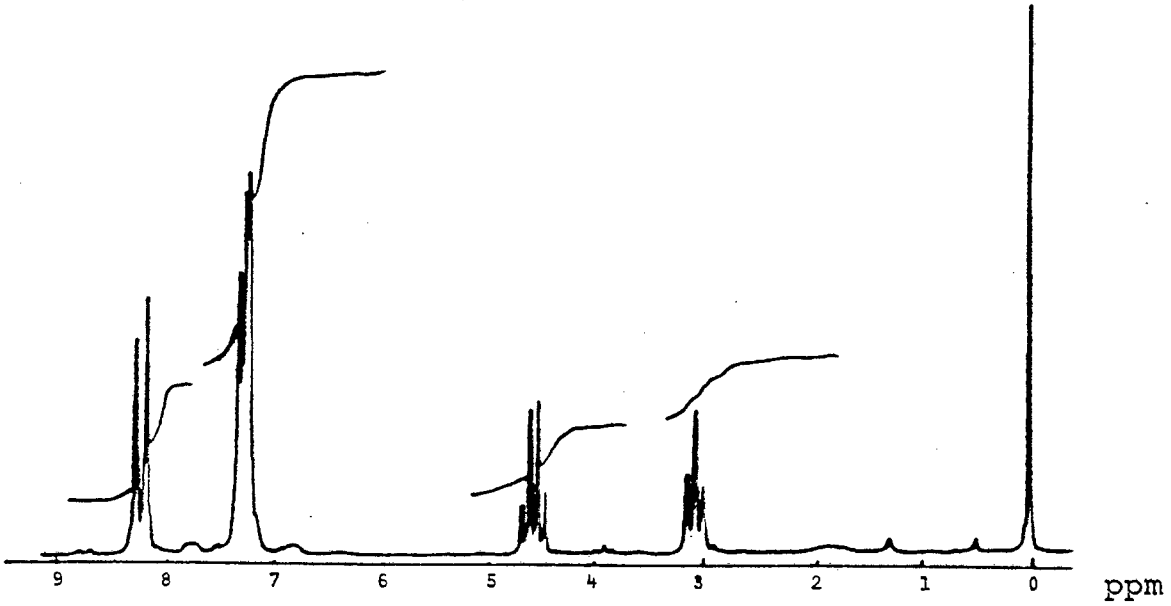
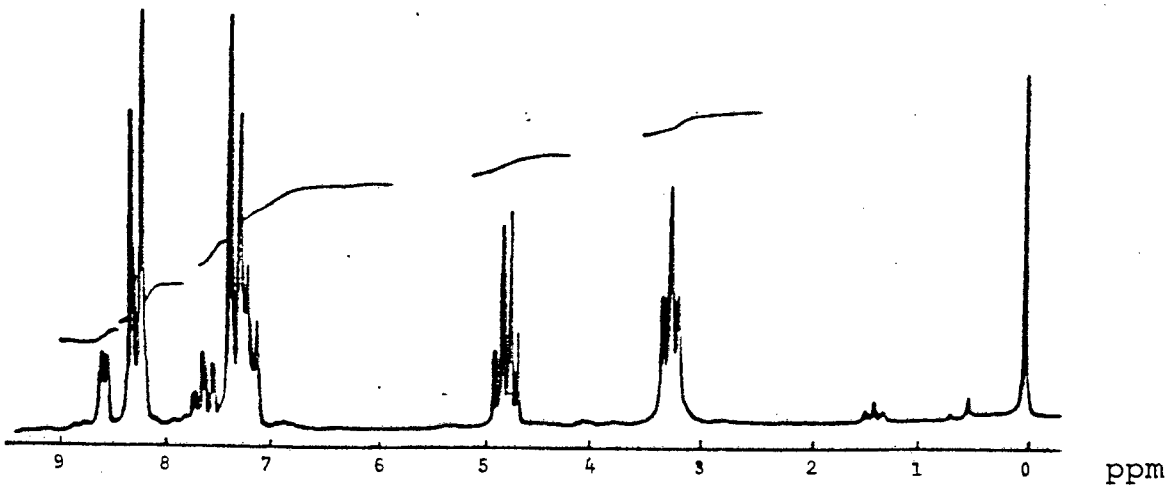


Figure 2.2 ^{1}H NMR spectrum of bis-(p-nitrophenyl)-[β-(2-pyridylethyl)] phosphate, 2.1c



respectively, relative to their chemical shifts in the phenyl analogue 2.1d is due to the electron withdrawing effect of the pyridyl nitrogen atom in 2.1c.

2.3 HYDROLYSIS OF THE BIS-(p-NITROPHENYL) PHOSPHATE ESTERS

2.3.1 INTRODUCTION

It was decided to compare the kinetics of the alkaline hydrolysis of substrates 2.1a-f in an attempt to establish whether or not the effect of the nitrogen in the pyridyl or quinolyl rings causes an enhanced rate of hydrolysis which could be attributed to intramolecular nucleophilic catalysis. For all substrates 2.1a-f alkaline hydrolysis can be expected to result in selective cleavage of the P - OPNP bond.[17] In general terms, the observed rate constant, k_ψ, for the hydrolysis can be expressed in the following way:

$$k_\psi = k_{H_2O}[H_2O] + k_{OH^-}[OH^-] + k_{H_3O^+}[H_3O^+] \qquad (2.7)$$

We selected conditions such that pH > pk_a p-nitrophenol (7.15)[18] (this precludes the possibility of the p-nitrophenol released existing in the undissociated form). Under these conditions, the $k_{OH^-}[OH^-]$ term predominates and the $k_{H_3O^+}[H_3O^+]$ term is negligible. The concentration of hydroxide ion was considerably in excess of the concentration of phosphate ester in these experiments to ensure the hydrolysis was pseudo-first-order in phosphate ester.

$$\text{Rate} = k_\psi[\text{phosphate ester}] \qquad (2.8)$$

In the preliminary spectral investigations, the absorption spectra

of 2.1a-f were recorded between 500 and 200 nm in order to establish a suitable wavelength with which to follow the progress of hydrolysis. A comparison of the UV absorption spectra of the phosphate esters 2.1a-f, originating from $\pi - \pi^*$ transitions of the aromatic ring showed no significant differences in wavelength maxima. The fact that the phosphate esters have the p-nitrophenyl group present has the advantage that the hydrolysis reaction rate may easily be followed spectrophotometrically. Base-catalysed hydrolysis of substrates 2.1a-f causes P - O bond cleavage releasing the p-nitrophenolate anion. At 400 nm this anion ($PNPO^-$) has spectral properties quite different from the reactants. Reaction rates were therefore measured by following the release of the $PNPO^-$ ion at its absorption maximum. The wavelength at which the greatest absorbance change occurred was at 400 nm and the kinetically isolable and stable p-nitrophenoxide ion is the only absorbing species at 400 nm. Under these conditions, the rate of $PNPO^-$ appearance represents the rate of hydrolysis of the substrate. The validity of Beer's Law ($A = \Sigma c\ell$) over the p-nitrophenol concentration encountered during a typical kinetic run was investigated prior to any kinetic studies. Beer's Law was found to apply over the given concentration range, thus justifying the use of absorbance at a fixed wavelength as a measure of p-nitrophenoxide concentration.

For all substrates, pseudo-first-order rate constants were calculated from the slopes of the plots of $\ell n(A_{a\infty} - A_t)$ values against time where $A_{a\infty}$ and A_t represent absorbances at the completion of hydrolysis and at time t, respectively. Second-order rate constants, k_{OH^-}, were obtained from the slope of the plot of the pseudo-first-order rate constants against hydroxide ion concentration, according to eq. 2.9.

$$k_{\psi} = k_{OH^-}[OH^-] + k_{H_2O} \qquad (2.9)$$

The rates of spontaneous hydrolysis (k_{H_2O}) were obtained from the intercepts of plots of k_{ψ} values versus hydroxide ion concentration. In the case of the simple esters 2.1b, 2.1d and 2.1f, k_{H_2O} should represent the rate constant for the hydrolysis by water alone, but for substrates 2.1a, 2.1c and 2.1e, this hydroxide ion independent term should also include any catalytic effects resulting from the presence of nitrogen in the ring.

2.3.2 RESULTS

The experimentally determined pseudo-first-order rate constants for the alkaline hydrolysis of substrates 2.1a-f calculated from the plots of $\ell n(A_{a\infty}-A_t)$ versus time for a series of solutions of different sodium hydroxide concentrations are summarized in table 2.1. There was good agreement between the experimentally determined pseudo-first-order rate constants and those obtained from the half life ($t_{\frac{1}{2}}$) using the formula $k = \ell n2/t_{\frac{1}{2}}$. The pseudo-first-order rate constants for the release of p-nitrophenoxide are proportional to the hydroxide ion concentration in the range studied. The values for the bimolecular rate constants and the spontaneous rate constants are summarized in table 2.2. The contribution of the hydroxide ion independent rate term to the overall rate of hydrolysis is very small. These values are, however, diagnostically important only in so far as a comparison between the nitrogen containing derivatives and their non-nitrogen analogues are concerned.

Table 2.1 Observed Rate Constants for the Hydrolysis of 2.1a-f in Aqueous NaOH at 25°C

[NaOH] M	$10\ k_{\psi}{}^{a}(s^{-1})$					
	2.1a	2.1b	2.1c	2.1d	2.1e	2.1f
0.0100		1.39	4.79	0.75		0.68
0.0080				0.62		
0.0075	12.33	1.08				0.53
0.0050	8.77	0.80	2.59	0.45	2.79	0.34
0.0037	6.42	0.66	1.80		2.38	0.29
0.0025	4.45	0.52	1.20	0.20	1.59	0.19
0.0016				0.13	1.27	
0.0010			0.51		0.91	

[a] Average from 2-3 runs; ± 6%

Table 2.2 Specific and Spontaneous Rate Constants for the Hydrolysis of 2.1a-f

Substrate	$10^{2}k_{OH^-}(s^{-1}M^{-1})$	$10^{3}k_{H_2O}(s^{-1})$
2.1a	160	36
2.1b	11.5	14
2.1c	47.8	3.2
2.1d	7.5	1.8
2.1e	47.8	0.46
2.1f	6.5	0.03

The results included in table 2.2 must be considered from two points of view. Firstly, a comparison between the three heterocyclic derivatives directly reflects the proximity effect of the pyridyl or quinolyl nitrogen atoms. The average relative results for the observed rate constants, the k_{OH^-} values and the k_{H_2O} values for the three pairs of substrates, 2.1a and 2.1b, 2.1c and 2.1d and 2.1e and 2.1f, are given as entry numbers 1, 2 and 3, respectively in table 2.3. The data indicates that under the same conditions, the heterocyclic derivatives are hydrolysed faster than their carbocyclic analogues. Rate acceleration exists for both the base-catalysed and spontaneous hydrolysis, although the former is more pronounced in the pyridyl heterocycles. In fact the results for 2.1a and 2.1c show no conclusive evidence for neighbouring group participation by the pyridyl nitrogen - the relative rate enhancement in the spontaneous rate term being merely 2.6 and 1.8, respectively. These solvolysis parameters imply a greater sensitivity of the specific rate constant k_{OH^-}, than the spontaneous rate constant k_{H_2O}, to the structural variation in the ester group (pyridyl versus phenyl). However, for the quinolyl/naphthyl pair 2.1e/2.1f, a k_{rel} = 14.8 value for the spontaneous hydrolysis is more significant than the $k_{rel}OH^-$ term (7.4). There is an observed 7-fold increase in the k_{OH^-} value for the quinolyl derivative relative to the napthyl derivative and this most likely results from the inductive effect of the quinolyl nitrogen. If the "general" rate-accelerating effect resulting from the inductive effect of the ring nitrogen were to be subtracted from the $k_{rel}H_2O$ value for the 2.1e/2.1f pair, "spontaneous" hydrolysis of 2.1e would still be *ca.* two times as fast as that of the napthyl compound 2.1f.

Table 2.3 Relative Rate Constants for pairs of phosphate esters

Substrate Pair		k_{rel}^{ψ}	$k_{rel}^{OH^-}$	$k_{rel}^{H_2O}$
1	2.1a/2.1b	8.5 - 13.8	13.9	2.6
2	2.1c/2.1d	4.8 - 6.3	6.4	1.8
3	2.1e/2.1f	8.3	7.4	14.8
4	2.1a/2.1c	-	3.3	-
5	2.1a/2.1e	-	3.3	-
6	2.1b/2.1d	-	1.5	-
7	2.1b/2.1f	-	1.8	-

Although the intramolecular catalytic effect of the nitrogen is greater in phosphoric diesters than triesters - Loran and Williams[14] report a 350-fold enhancement for the analogous diesters, we believe that an intramolecular catalytic effect (although less significant) exists in the hydrolysis of bis(p-nitrophenyl) quinolin-8-yl phosphate. It is worthwhile to consider the electronic nature of the reactive species involved in these reactions. For the substrates 2.1a-f it could be expected that the k_{OH^-} term be greater than the k_{H_2O} term as the former involves the attack of a strong negatively charged species at a neutral centre (i.e. involves an ion-dipole interaction). The k_{H_2O} term, however, requires a dipole-dipole interaction. The intermolecular approach of the charged nucleophile (OH^-) at the also negatively charged diester derivative would be electrostatically unfavourable and indeed no specific rate term (k_{OH^-}) was observed by Loran and Williams. Contrary to the neutral triester, the intramolecular reaction is favourable in the diester (it involves an ion-dipole interaction).

Secondly, a comparison down the series, between the nitrogen containing derivatives provides information regarding the intrinsic nucleophilicity and/or the inductive effect of the heterocyclic atom on the dynamics of the phosphate ester group. These particular relative values are given in table 2.3. The $k_{rel}OH^-$ value of 3.3 for the 2-pyridiylmethyl (2.1a) to β-(2-pyridyl)-ethyl (2.1c) derivatives (entry number 4) is typical of the "fall-off factor"[19] resulting from the insertion of an additional methylene link between the two functional centres in 2.1c. Substituent constants, as measured by Taft's constant σ* (inductive effect) decrease by a factor of *ca.* 2.8 every time they are moved one methylene group

further from the reaction centre.

Coincidently, the specific rate constants for the β-(2-pyridyl)-ethyl and 8-hydroxyquinolyl derivatives are the same and subsequently the $k_{rel}OH^-$ value for the substrates 2.1a to 2.1e is also 3.3 (entry number 5). Steric rather than electronic effects are probably responsible for this and the result may reflect the greater conformational flexibility in the pyridyl compound.

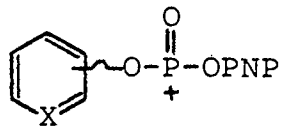
An analogous comparison down the series for the carbocyclic containing compounds follows the above trend: the $k_{rel}OH^-$ value of 1.5 for the benzyl (2.1b) to the β-(2-phenyl)-ethyl (2.1d) derivative (entry number 6) results from the electron withdrawing effect of a phenyl versus methylene group; the $k_{rel}OH^-$ value of 1.8 for the benzyl (2.1b) to the naphthyl (2.1f) derivative (entry number 7) reflects the steric bulk of the latter system.

Finally, because the ability of the pyridyl or quinolyl nitrogen atoms to interact with the phosphoryl centre would certainly be reduced in an aqueous medium because of hydrogen bonding to water, it was of interest to examine the behaviour of these phosphoric triesters in the gas phase under conditions of electron impact-induced fragmentations.

2.4 MASS SPECTROMETRY OF COMPOUNDS 2.1a-f

Besides the kinetic study of the alkaline hydrolysis of substrates 2.1a-f, a comparative study of the mass spectra of these compounds seemed to be a useful probe for determination of the effect, if any, the nitrogen heteroatom might have on their fragmentation patterns under conditions of electron impact.

The fragmentation most relevant to our discussion of the kinetics of the alkaline hydrolysis of 2.1a-f is the fragmentation involving loss of the p-nitrophenoxy radical species (PNPO$^{\bullet}$) which generates the phosphorylium ion 2.4.



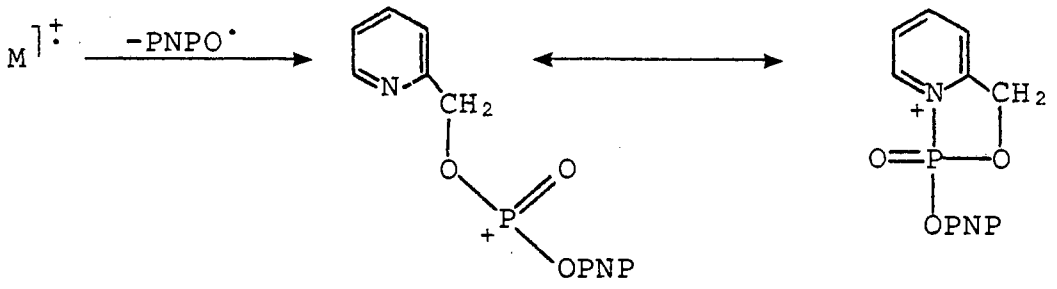
2.4

X = N, CH

~ = variable molecular linkage

Results related to this fragmentation are collected in table 2.4. Since phosphorylium ions are generally considered as unstable species, low intensity of the (M-PNPO$^{\bullet}$) peaks was anticipated for all compounds studied. The intensities of the M-PNPO$^{\bullet}$ peaks could therefore provide a direct measure of the stabilities of the phosphorylium ions generated during this fragmentation.

The most striking features of the mass spectrum of substrate 2.1a in contrast to that of 2.1b, are the absence of a molecular ion (m/e 431) and the appearance of a peak at $M-138]^{+}$ (relative abundance 13%) resulting from the expulsion of a p-nitrophenoxide radical. We propose that this difference results from the fact that the phosphorylium ion so formed (2.5) can be stabilized by resonance (eq. 2.10).



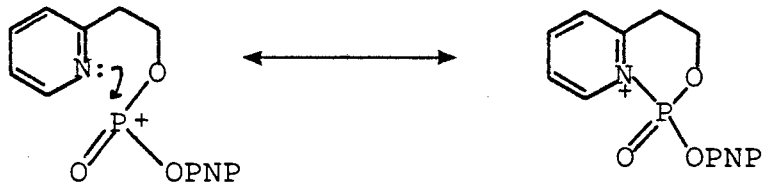
(2.10)

2.5 phosphorylium ion

2.6 pyridinium ion

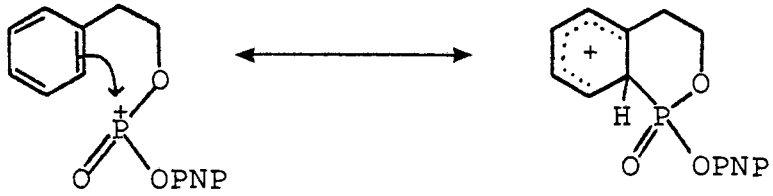
Direct cleavage of the P-OPNP bond with loss of the PNPO· radical was not observed for the benzyl derivative 2.1b.

For both substrates 2.1c and 2.1d, the M-PNPO·]+ species are barely detectable - relative intensity 0.45 and 0.24%, respectively. This is due mainly to the favourable McLafferty type rearrangement[20] (discussion follows) rather than to an unstable phosphorylium ion formation. We think that the stabilities of the cyclic 5-membered (2.6) and cyclic 6-membered (2.8) pyridinium ions resulting from the expulsion of the p-nitrophenoxy radical in substrates 2.1a and 2.1c are not greatly different. The relative intensity of 13% versus 0.45% for these two compounds reflects rather the additional fragmentation pathway available to 2.1c. Nevertheless, we can postulate the following resonance stabilization for the phosphorylium ions corresponding to 2.1c and 2.1d (eqs. 2.11 and 2.12, respectively).



(2.11)

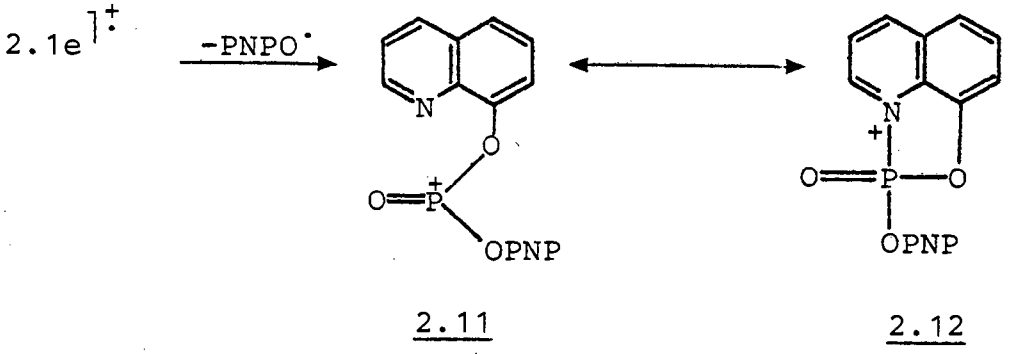
2.7 2.8



(2.12)

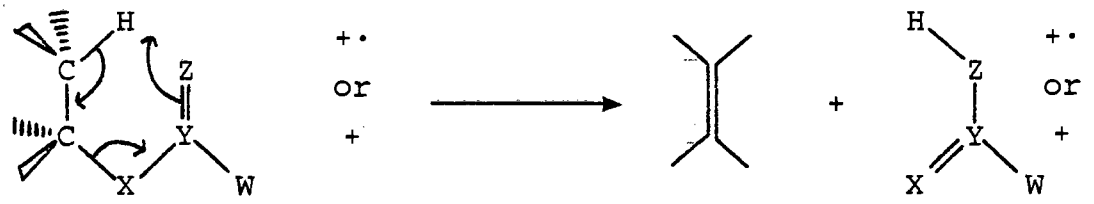
2.9 2.10

During the alkaline hydrolysis of our substrates, only the quinolyl derivative demonstrated any intramolecular catalytic effect. Although in the gas phase, we have seen evidence (albeit minor) for an intramolecular interaction of the pyridyl nitrogens with the phosphoryl centre, once again it is the quinolyl derivative which provides the most striking result. The solvolytic trend is fully paralleled in mass spectrometry. There is a dramatic difference in the fragmentation behaviour of the quinolyl and naphthyl compounds. For the nitrogen containing heterocycle, the molecular ion is very unstable (relative abundance 7%) but has as the base peak, the phosphorylium ion m/e 329, formed by loss of the PNPO$^{\cdot}$ species. The naphthyl analogue, however, has the molecular ion as its base peak and loss of the PNPO$^{\cdot}$ species gives a signal with relative intensity of only 4.6%. Quite clearly intramolecular interaction of the quinolyl nitrogen with the phosphoryl centre contributes to the loss of the PNPO$^{\cdot}$ species (P - O bond cleavage) and the resulting phosphorylium ion (2.11) can be resonance stabilized (eq. 2.13).

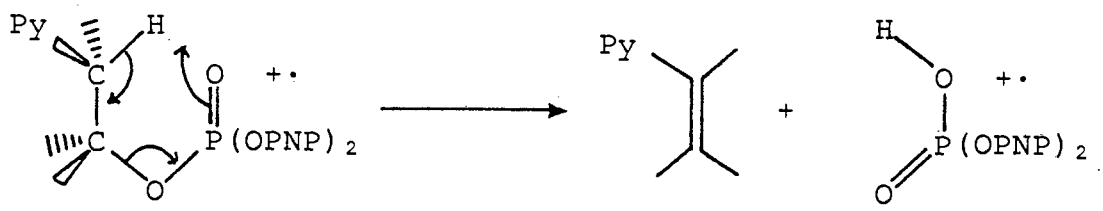


2.11 2.12 (2.13)

In a different domain, the behaviour of substrate 2.1c in the gas phase parallels to a degree that observed in solution chemistry where 2-vinylpyridine is formed as an elimination product. Loss of 2-vinylpyridine from 2.1c occurs via the typical McLafferty rearrangement to give a peak at m/e 340 corresponding to the radical ion of the bis-(p-nitrophenyl) phosphoric acid - $(PNPO)_2PO_2H]^{+\cdot}$. McLafferty rearrangement operates for ions (or radical ions) capable of electronic shift involving a 6-membered cyclic transition state in the following molecular skeleton. The general reaction for the H-type rearrangement is given in eq. 2.14 but as applied to substrate 2.1c , is shown in eq. 2.15.



(2.14)



(2.15)

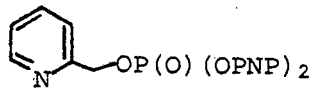
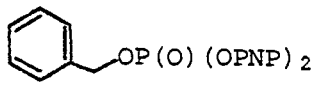
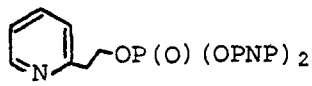
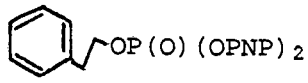
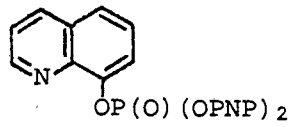
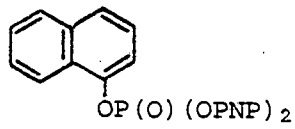
2.1c

Py = α-C_5H_4N

Mass spectral studies of the triesters 2.1a-f show rich and complex fragmentation behaviour,[21] involving the phosphate group, as well as the ester substituents and often requiring hydrogen atom rearrangements. However, only the fragmentation involving direct P-OPNP cleavage has been discussed as this is the most relevant to the solvolytic studies.* In all the nitrogen containing derivatives there was evidence (although minimal for 2.1c), for a "donor-accepter" interaction between the nitrogen atom and the electron deficient phosphoryl centre.

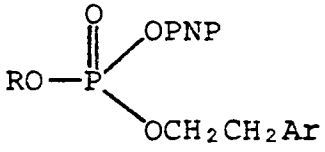
*For some additional fragmentations, see ch. 9.4.

Table 2.4 Selected Fragmentation Data for 2.1a-f

Substrate	Molecular ion m/e	Relative Intensity	$M^{+\cdot}$ - PNPO· m/e	Relative Intensity
2.1a 	431	-	293	13%
2.1b 	430	3%	292	-
2.1c 	445	-	307	0.45%
2.1d 	444	-	306	0.24%
2.1e 	467	7%	329	100%
2.1f 	466	100%	328	4.6%

2.5 SYNTHESIS OF MIXED TRIESTERS OF PHOSPHORIC ACID

In the preceding section, a number of compounds of type 2.1 have been synthesized and the preliminary results on their base-catalysed hydrolysis obtained and compared with their carbocyclic analogues. However, because of the possible problems caused by the second 4-nitrophenyl ester group in the starting materials, we turned our attention to developing another model, (2.13) - a mixed asymmetric triester for structure reactivity studies.



2.13

R = Me, Et, Ph

Ar = Ph, α-C_5H_4N

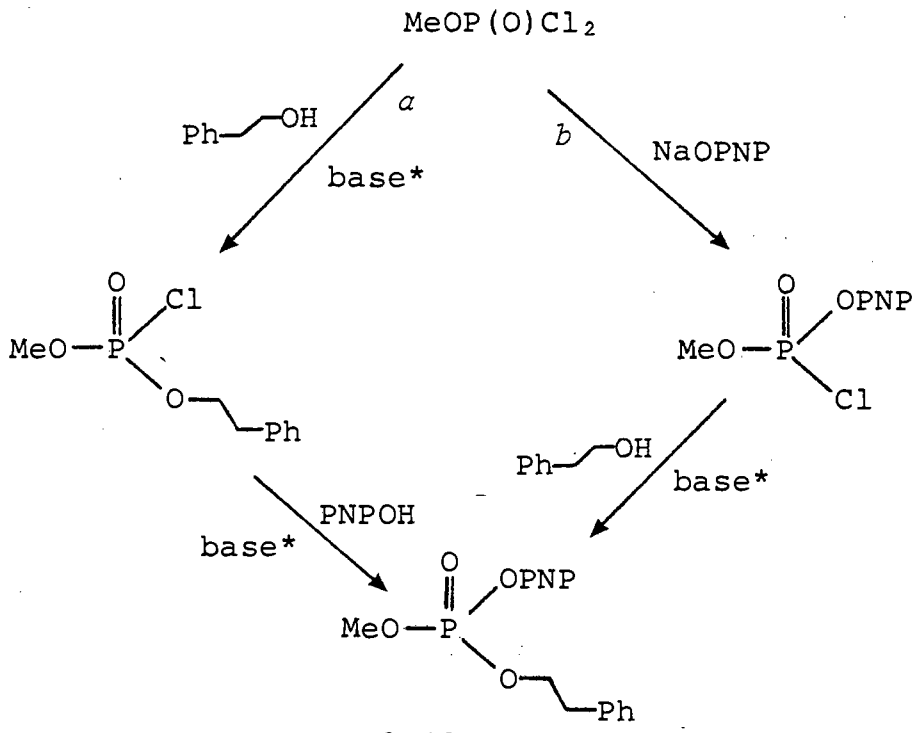
The available information concerning the synthesis of neutral asymmetrical triesters of phosphoric acid is scarce. In 1964 a report appeared in the literature by Dilaris and Eliopoulos[22] concerning the synthesis of fully esterified phosphates with dissimilar groups attached to phosphorus.[23] Prior to this, only a few cases of neutral asymmetrical esters had been reported - mostly in the field of phospholipid synthesis. Dilaris and Eliopoulos experienced great difficulties in their efforts to synthesize phosphate esters of type $(R_1O)(R_2O)(R_3O)PO$ even with simple alkyl or aryl R groups. Their greatest problems lay in the actual isolation of the product triester from the reaction mixture and this they finally attributed to the high instability of these asymmetrical neutral esters. Stability, in fact, was only expected if the compounds were isolated as crystalline materials of high purity. Only three

such compounds were obtained: p-nitrobenzyl p-bromobenzyl phosphoglycolic acid, phenyl p-cresyl phosphocholine sulphate and phenyl p-cresyl N,N-dimethylaminoethyl phosphate tetraphenylborate. In the syrup-like or liquid (non-crystalline) triesters, it was suspected that the last traces of impurity accelerated molecular transformations and interchange of the different ester groups and this led to intractable polymeric materials.

Since 1964, there has been a growing interest in the synthesis of asymmetrical phosphate triesters. One of the main reasons for this has been the recognition of the usefulness of the phosphotriester approach in nucleic acid[24] and phospholipid synthesis. Mixed trialkyl phosphates are also of current interest in the area of pesticides.[25] Clearly asymmetrical triesters have established a niche (biochemical/biological/chemical) in a diversity of fields. Our interest, however, in compounds of general formula 2.13 (Ar = α-C_5H_4N) arose because of their potential for structure reactivity studies.

The ester 2.13a (R = Me, Ar = Ph) was the initial target compound and the synthesis was attempted following two synthetic pathways (pathway *a* and *b* in scheme 2.2).

Scheme 2.2



2.13a

*base = triethylamine or pyridine.

The first step of the reaction represented by pathway *a* was carried out by the dropwise addition of an etheral solution of 2-phenylethanol and triethylamine (1:1) over a 1 h period to a cooled ethereal solution of methyl phosphorodichloridate. The reaction mixture was stirred overnight at room temperature. The white precipitate which had formed was collected by filtration and examined by ^1H NMR (D_2O) spectroscopy. The spectrum was consistent with N-methylated triethylammonium chloride (N-methyl singlet at δ4.47). The starting alcohol was recovered from the organic fraction after removal of the ether under vacuum. This result can be explained in terms of demethylation of the organophosphorus substrate by triethylamine.

$$MeO\text{-}P(O)Cl_2 + Et_3N \longrightarrow Et_3NMe^+(Cl_2PO_2^-) \qquad (2.16)$$

In an attempt to prevent the demethylation of the substrate, we decided to follow a method reported by Bromilow *et al.*[26] which involved first, the reaction of the phosphorodichloridate with sodium p-nitrophenoxide. This is shown in pathway *b* in scheme 2.2 We were aware of the possibility of demethylation of the ester by the p-nitrophenoxide anion but monitoring the reaction progress by TLC revealed that no p-nitroanisole was formed. The reaction involved refluxing a benzene suspension of sodium p-nitrophenoxide and a 20% excess of methyl phosphorodichloridate for 4 h. After filtering the sodium chloride, the excess of phosphorylating agent was removed *in vacuo* under reduced pressure. The residual product was characterized by ^{1}H NMR ($CDCl_3$) spectroscopy and used without further purification in the second step of the reaction. Methyl-(p-nitrophenyl) phosphorochloridate was dissolved in a minimum volume of dry benzene and added slowly to an ice-bath cooled and stirred solution of 2-phenylethanol in pyridine. The reaction mixture was allowed to stir at room temperature overnight. A fine white precipitate was observed in the straw coloured solution. The mixture was taken up in 30 ml ether and 15 ml water. The aqueous layer was separated and extracted with three 10 ml aliquots of ether. The combined organic extracts were dried and the solvent was removed by evaporation to give a yellow oil. The ^{1}H NMR ($CDCl_3$) spectrum showed this to be mainly unreacted β-(2-phenyl)-ethanol. After removing the water from the aqueous extract by evaporation, a white precipitate was obtained. The ^{1}H NMR spectrum revealed that demethylation by the base was again complicating the reaction (a singlet at δ4.08 was assigned to the N-methyl pyridinium species).

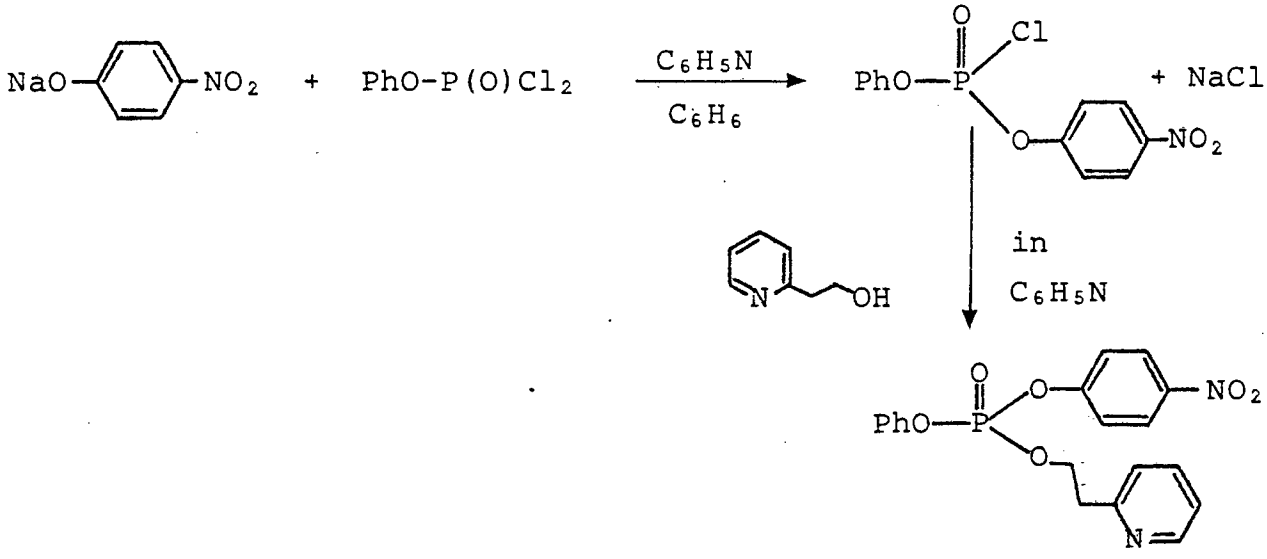
Since it was evident that the methyl group contained in the target ester 2.13, was a reason why the synthesis of this compound was proving difficult - nucleophilic attack at the methyl carbon of the phosphorochloridate was faster than oxygen attack by the alcohol at the phosphorus centre, we formulated a new target molecule - compound 2.13b (R = Et, Ar = Ph). It was hoped that the introduction of the ethyl group at phosphorus would free the synthesis from the complicating dealkylation reaction.

The synthesis of 2.13b was attempted in an analogous manner to 2.13a (pathway *a*). The excess of ethyl phosphorodichloridate was removed by distillation (34 - 40°C/0.5 mm - 1.0 mm Hg) and the second fraction was collected at between 45 - 140°C/0.5 - 1.0 mm Hg. A black residue remained in the distillation flask. The second fraction was found by ^{1}H NMR spectroscopy to consist of the desired product (74%) and 2-phenylchloroethane (26%). Identification of the latter product, which had not been observed in the ^{1}H NMR spectrum of the crude mixture, was proven by comparison with authentic material. A second distillation to separate the two components was attempted and again resulted in a lower boiling (44 - 47°/0.4 mm Hg) and a higher boiling (130 - 137°C/0.4 mm Hg) fraction. The first fraction corresponded to 2-phenylchloroethane and the second fraction to the desired product as well as some 2-phenylchloroethane. It then became apparent that distillation of 2.13b was not a suitable procedure for its purification as 2-phenylchloroethane was being produced during this thermal treatment. An investigation of this fragmentation is described in ch. 9. When repeating the synthesis, this problem was circumvented by distilling off only the excess of starting material. The distillation was carried out by gently

heating the reaction vessel and not allowing the temperature to rise above 50°C at reduced pressure. The success of the condensation reaction was evident from the ^{1}H NMR spectrum of the undistilled fraction and the product was further characterized by elemental analysis. In the final step of the synthesis, a suspension of p-nitrophenol in ether containing 2,6-dimethylpyridine, was added dropwise to a stirred solution of ethyl (2-phenylethyl) phosphorochloridate, maintaining the temperature below 10°C. The mixture was then stirred for 3.5 h at room temperature during which time a fine white precipitate of lutidinium chloride appeared in the solution. Despite filtration and centrifugation the ^{1}H NMR ($CDCl_3$) spectrum of the oil obtained after removing the ether by evaporation, showed contamination of the product by the salt. A chromatographic separation using a chloroform:acetone (9:1) mixture as eluant was effected, and although separation of the lutidinium chloride was achieved, both TLC and ^{1}H NMR spectroscopy revealed that the ester was unstable under these conditions, releasing large quantities of p-nitrophenol.

Discouraged with these synthetic results, we reformulated the target compound as 2.13c (R = Ph, Ar = αC_5H_4N). The synthesis was first attempted as outlined in scheme 2.3. The procedure of Bromilow *et al.*[26] was repeated for the preparation of p-nitrophenyl phenyl phosphorochloridate. Dried sodium p-nitrophenoxide was suspended in benzene and to this was added a benzene solution of phenyl phosphorodichloridate. The mixture was refluxed for 4 h during which time the red/orange colour of sodium p-nitrophenoxide gradually disappeared and a white precipitate of sodium chloride formed.

Scheme 2.3



2.13c

Filtration of the precipitate and evaporation of the benzene yielded a yellow oil. This was distilled at 250°C (0.5 mm Hg) and a sand coloured oil which solidified on addition of petroleum ether, was obtained. (A black residue was left in the distillation flask.) Recrystallization from benzene produced very fine crystals, m.p. 105 - 107°C. The melting point of p-nitrophenyl phenyl phosphorochloridate has been reported as 78 - 80°C.[22,27] These groups of workers also report the melting point of the acid - p-nitrophenyl phenyl hydrogen phosphate as 101 - 102°C[22] and 99°C,[27] respectively. The high melting point which we obtained suggested that the acid, not its chloride was present. The elemental analysis for the product did not correspond to the expected chloride but rather to the acid, or P^1,P^2-diphenyl-P^1,P^2-di(p-nitrophenyl) pyrophosphate. The latter compound could easily have formed from the chloride and the acid, as a result of partial hydrolysis. The ^1H NMR spectrum was not particularly informative as both the spectral pattern and the intergrated areas for the acid, 2.13c and the pyrophosphate would be indistinguishable. No signal corresponding to the

hydroxyl absorption was found.

When this synthesis was repeated with strict attention being given to rigorously drying the reagents and excluding moisture throughout the reaction, exactly the same product was obtained. We are convinced that the obtained product (probably the symmetrical pyrophosphate) results from the thermal disproportionation of the phosphorochloridate, rather than from its hydrolysis. Fragmentation and disproportionation of a variety of phosphoric derivatives (including phosphorochloridate) have been observed before,[28] and the polyphosphoric systems are the most common products of these reactions. Thermal degradation of phosphorochloridates will be discussed in a following chapter. Unable to obtain pure phenyl (p-nitrophenyl) phosphorochloridate, we abandoned the approach to 2.13c shown in scheme 2.3.

The procedure reported by Dilaris *et al.*[22] for the synthesis of p-nitrophenyl phenyl phosphorochloridate is based on the phosphorylation of phenol by p-nitrophenyl phosphorodichloridate in the presence of sodium chloride. So in the second approach to synthesize p-nitrophenyl phenyl phosphorochloridate, the order of introducing the various substituents at phosphorus was changed, i.e. p-nitrophenol was introduced first. p-Nitrophenyl phosphorodichloridate was obtained by refluxing p-nitrophenol in an excess of phosphorus oxychloride using sodium chloride as a catalyst. We followed the method described by these workers up to the point of isolating the product, *viz.* a mixture of p-nitrophenyl phosphorodichloridate, phenol which was added in small portions, and dry sodium chloride (in a 0.11:0.10:0.02 molar ratio) was heated

in an oil bath for 6h, during which time the temperature was slowly increased to 170°C. The reaction vessel was cooled and the volatile products removed under reduced pressure. Although Dilaris obtained a fraction boiling at 203 - 209°C (1 mm Hg), because of the difficulties described in the previous section, we decided to use the product without further purification. The ^{1}H NMR spectrum of the crude product indicated that it was reasonably pure. The dissymmetric phosphorochloridate was dissolved in benzene and slowly added to an ice-bath cooled and stirred solution of β-(2-pyridyl)-ethanol in pyridine. Stirring was continued at room temperature for 18 h but no precipitate of pyridinium chloride was observed. The mixture was taken up in a large volume of ether and water, the aqueous layer was separated and extracted three times with ether and the combined organic extracts were dried and concentrated to an oil. The ^{1}H NMR spectrum of the crude mixture showed the characteristic quartet and triplet indicative of the P-OCH_2CH_2 grouping. As pyridine was still present, three aliquot portions of benzene were added to the product and the solvents co-evaporated after each addition. The reaction flask was left in a dessicator over concentrated sulphuric acid in order to remove the last traces of pyridine. Purification by column chromatography using chloroform as eluant produced the pure product - but in low yield as again decomposition of the product with the release of p-nitrophenol was observed.

One final attempt to synthesize the target compound of general formula 2.13 was carried out using a completely different approach which was based on the transesterification of a triester containing two p-nitrophenyl groups, according to eq. 2.17.

$$(PNPO)_2P(O)OR \xrightarrow[-PNPO^-]{MeO^-} PNPO(MeO)P(O)OR \qquad (2.17)$$

When a stoichiometric equivalent of sodium methoxide (as a suspension in petroleum ether) was added to bis-(p-nitrophenyl)(β-phenylethyl) phosphate in benzene and the mixture stirred for 4 h at room temperature, the monosubstituted product 2.13d (R = $PhCH_2CH_2$), the disubstituted product 2.14, sodium p-nitrophenoxide and p-nitrophenol were recovered from the reaction mixture (eq. 2.18).

$$(PNPO)_2P(O)OR \xrightarrow[-PNPO^-]{k_2} \underset{\text{2.13d}}{PNPO-\overset{\overset{O}{\|}}{\underset{\underset{OMe}{|}}{P}}-OR} \xrightarrow[-PNPO^-]{k_2{}^1} \underset{\text{2.14}}{(MeO)_2P(O)OR} \qquad (2.18)$$

After filtering off the sodium p-nitrophenoxide and removing the solvents, a yellow oil was obtained. Analysis of the ^1H NMR ($CDCl_3$) spectrum showed two P-O-methyl doublets ($^3J_{H,P}$ 11 Hz) at δ3.70 and δ3.80 which we tentatively assigned to the di-methyl and mono-methyl substituted products respectively. Free p-nitrophenol was identified by the appearance of a doublet at δ6.97 for the two aromatic protons β to the NO_2 group. Although the kinetics of the reaction (eq. 2.18) was not investigated, we believe that $k_2{}^1 > k_2$ as further experiments designed to isolate 2.13d during the reaction were unsuccessful. Separation of 2.13d from 2.14 by column chromatography was not satisfactory because of the unstable PNPO-P bond and the final yield of 2.13d based on the starting triester was only 11%. The mono-methyl triester was characterized by ^1H NMR spectroscopy and the doublet at δ3.80 for the methyl group intergrated for three protons.

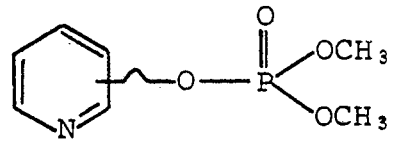
In conclusion, we have found no satisfactory method for the preparation of asymmetrical triesters containing one 4-nitrophenyl ester substituent. We attribute this partly to the thermal instability of the intermediates and partly to the unstable nature of the fully esterified p-nitrophenyl phosphate. In addition, because of the difficulty experienced in isolating the intermediates, they were used in the second condensation step of the reaction sequence in an impure form which then rendered subsequent isolation of the product even more difficult. Several attempts to purify the phosphorylated products by chromatography have failed because of the ease with which the PNP-O bond cleaves. Our work with methyl phosphate esters was complicated by the susceptibility of the methyl group to nucleophilic attack by any nucleophile present in the reaction mixture. Recently, the methyl group has been used as a protecting group for phosphodiesters during nucleotide synthesis, because it can be removed selectively under mild conditions. Our results confirm the labile nature of a methyl group under fairly mild conditions.[5,6,29] As some considerable effort has been directed towards the synthesis of mixed triesters without much success, we decided to reformulate our objective in favour of a dialkyl triester containing a nitrogen heterocycle in the third ester function - hence resembling a nucleotide structure (both alkyl groups = R). In contrast to asymmetrical phosphate triesters, there are numerous approaches to the synthesis of phosphate triesters, phosphinates and phosphonates reported in the literature[30] where at least two of the groups at phosphorus are the same. We were then interested in the possibility of intramolecular alkylation with the heterocyclic nitrogen acting as an internal nucleophile and work regarding this topic is contained in ch.s 3, 4, 5 and 6.

Chapter 3

Preparation of Selected Dimethylaryl and Dimethyl(arylalkyl) Phosphates

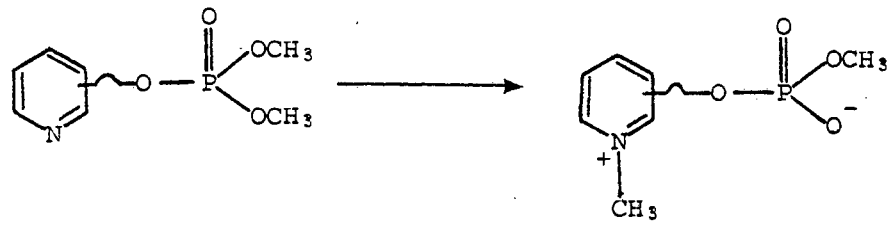
3.1 INTRODUCTION

In recent years, the direct N-alkylation of basic moieties of nucleic acids has been the subject of considerable chemical and biological interest.[4] Such reactions may not only be useful from a synthetic point of view but are also relevant to the study of mutagenic and carcinogenic effects occurring in living systems.[7] Alkylating agents have in fact been considered as an origin of mutagenic effects since alkylation may furnish the modified nucleotide units which are then no longer capable of performing the normal biological functions. With these aspects in mind we wished to study the reactivity of a class of compounds having the general formula 3.1.



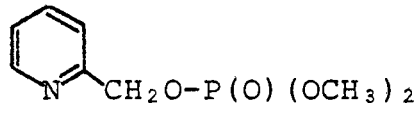
3.1

Besides the electrophilic phosphorus centre, an additional electrophilic centre (ester methyl group) has been introduced. In these systems an oxygen→nitrogen methyl transfer reaction can occur *via* the nucleophilic displacement of the methyl group by the pyridyl nitrogen atom. The reaction (eq. 3.1) can follow the inter- and/or intramolecular mechanism and the relative importance of these two pathways should be a function of various factors.

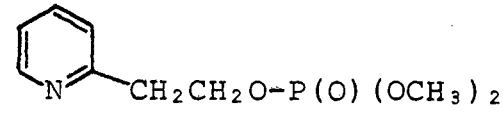


(3.1)

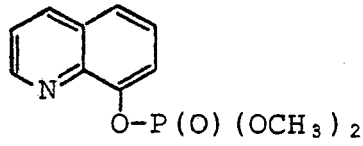
This chapter is concerned with the synthesis and the characterization of the compounds A, B, C and D.



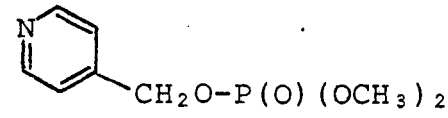
A



B



C

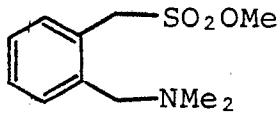


D

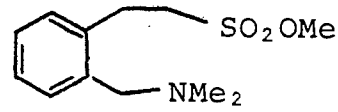
Besides investigating the nature of the methylation reaction (inter- vs. intramolecular process), our studies are also intended to establish the following: the correlation of the reactivity of substrates A-D with their detailed structure; and the medium effect on the kinetics of the reaction. These topics are discussed

in the following chapters (ch.s 4 and 5).

The triester A was chosen as a model substrate because not only should its reactions due to steric reasons be free of any intermediate formation of the aziridinium ion, observed for aliphatic β-aminoalkyl esters,[10] but also because in view of a recent report on selectivity in dealkylation of phosphate esters,[29] competing alkylation by the 2-pyridylmethyl group is not expected. If A is considered the initial target ester, then compound B contains an additional methylene unit which could illustrate the effect of chain length on the rate of the methyl transfer reaction. The strong dependence of intramolecular reactivity on chain length has been recognised.[31] For any nucleophilic displacement (also intramolecular displacement) to occur, the most favourable orientation of the nucleophile→electrophile-leaving group, is linear. This situation is more likely in a large ring, where less deviation from the ideal 180° orientation would take place. King and McGarrity[31] showed that O→N methyl transfer in 3.2 is exclusively intermolecular (an 8-membered cyclic-transition state is required for the intramolecular reaction), but in 3.3 it is partly intramolecular (a 9-membered cyclic-transition state is involved).

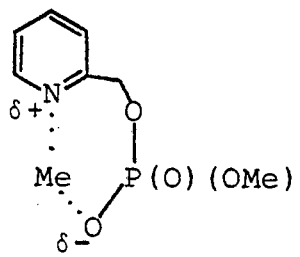


3.2

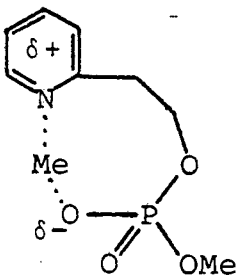


3.3

So if oxygen→nitrogen methyl transfer in A occurs intramolecularly *via* way of a 7-membered transition state, then it is postulated that oxygen→nitrogen methyl transfer in B should be more favourable as it would proceed *via* way of an 8-membered cyclic transition state. The proposed transition states for endocyclic nucleophilic displacement in A and B are shown as the 7- and 8-membered cyclic structures $A^{\dagger}$ and $B^{\dagger}$ respectively.



$A^{\dagger}$



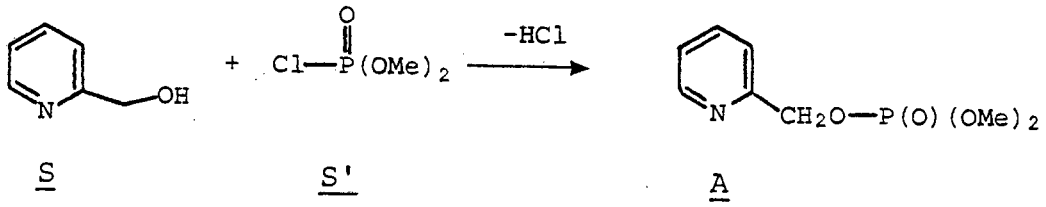
$B^{\dagger}$

Compound C is envisaged as providing a more rigid CH_3-OPOCCN skeleton which would enhance an intramolecular methyl transfer from the ester oxygen atom to the quinolyl nitrogen atom, if in fact the potential for such a transfer existed.

Compound D represents the dimethyl phosphate analogue derived from 4-pyridylmethanol. An intramolecular process for the methyl transfer reaction is very unlikely, if not impossible, as the nitrogen atom is too far removed from the methyl ester phosphate group.

3.2 SYNTHESIS OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE (A)

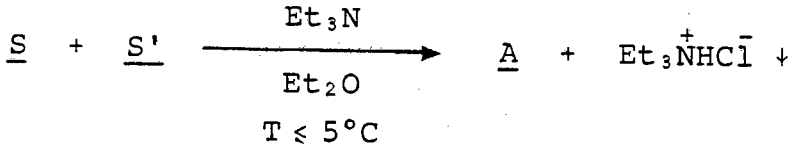
The substrates used for this synthesis were 2-pyridylmethanol, S, and dimethylphosphorochloridate, S'. The general reaction can be represented by eq. 3.2.



S S' A (3.2)

Four different routes to the synthesis of the target molecule were attempted, with varying degrees of success.

3.2.1 SYNTHESIS INVOLVING TRIETHYLAMINE AS A BASE



S + S' → A + $Et_3\overset{+}{N}H\overset{-}{Cl}$ ↓

To an ethereal solution of dimethylphosphorochloridate was added dropwise, with stirring and cooling in an ice/salt bath ($T \leq 5°C$), an equimolar mixture of 2-pyridylmethanol and triethylamine. A fine white precipitate was immediately formed. After the addition, the reaction mixture was stirred for a further two hours at this temperature and then left to stand overnight in a refrigerator. Thin layer chromatography (TLC) of the reaction mixture (acetone : chloroform; 7 : 3) showed no trace of

unreacted alcohol after this time. The white precipitate was removed by filtration, washed with ether and dried in a dessicator under vacuum. The ^{1}H NMR (D_2O) spectrum of this precipitate shows it to consist of $Et_3\overset{+}{N}H$ and $Et_3\overset{+}{N}Me$ ions in the ratio 9 : 1. A singlet at δ2.90 for the $\overset{+}{N}-CH_3$ absorption confirms that even at low temperature, triethylamine nucleophilically displaces a methyl group of the substrate (or product) phosphate. Removal of the ether *in vacuo* left a mixture of a white solid and an oil. The ^{1}H NMR ($CDCl_3$) spectrum showed this to consist of the product (A), protonated 2-pyridylmethanol, triethylamine hydrochloride, unreacted dimethylphosphorochloridate and dimethyl phosphate. The appearance of a symmetrical doublet at δ5.25 ($^3J_{H,P}$=8Hz) confirms the formation of the $-CH_2-O-P$ bond. This splitting of the $-CH_2-$ signal is due to coupling of the methylene protons with the ^{31}P nucleus. The $R-CH_2-O-P$ grouping has a coupling constant range 6.5 - 10 Hz.[32] The downfield shift relative to the singlet (δ4.77) in the spectrum of the alcohol, S, is a result of the electron withdrawing effect of the phosphoryl group. Both of these factors provide a useful probe for the successful coupling of 2-pyridylmethanol to the phosphorylating agent. The absence of a singlet at δ4.77 confirms there is no unreacted alcohol in the mixture. This signal has, however, shifted downfield to δ4.9 (Δδ0.13 ppm) which suggests a more deshielding environment for these protons. There is no evidence for pyridyl nitrogen-methyl bond formation[33] which indicates that the positive charge on the nitrogen (causing deshielding) is due to protonation. This deshielding effect is more pronounced on the proton α to the pyridyl nitrogen and the doublet of doublets for this proton shifts downfield from δ8.43 to δ8.69 (Δδ0.26 ppm).

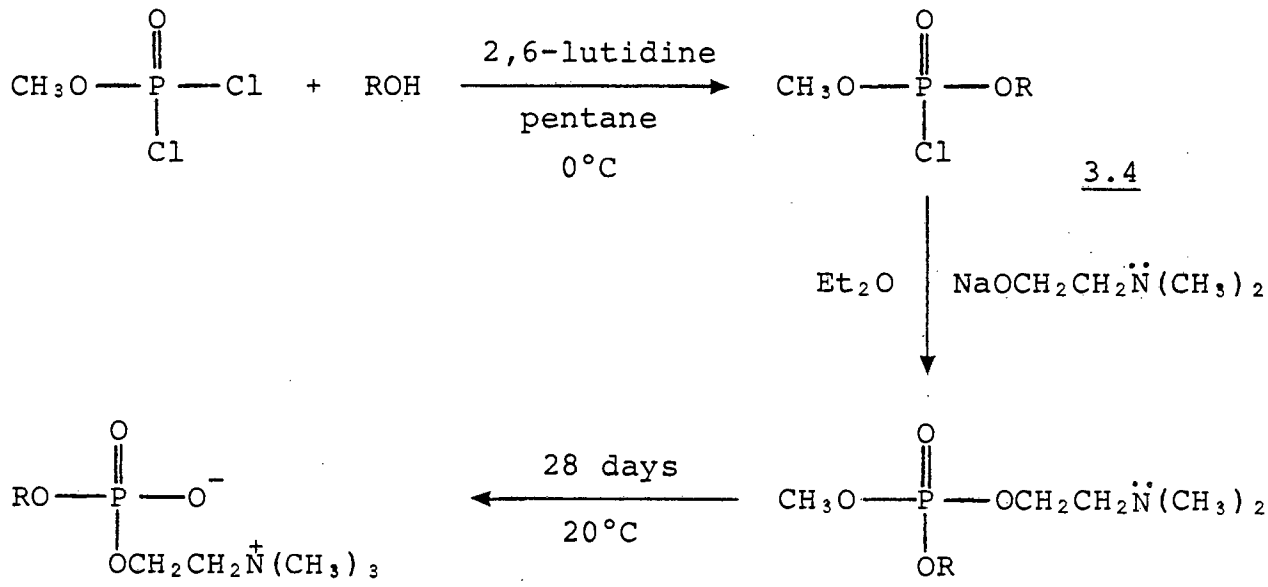
Unfortunately the ^{1}H NMR spectrum showed that the desired product was present to only 20% in the total reaction mixture. The ratio of product (A):protonated 2-pyridylmethanol was 3:4 which suggests that although triethylamine is *ca.* 10^5 x a more powerful base than 2-pyridylmethanol (pKa Et_3N (25°C) = 10.75;[34a] pKa C_6H_7ON (30°C) = 4.89[34b]), the substrate is still susceptible to protonation. The product mixture was found to be contaminated with triethylammonium chloride although filtration to remove it had already been effected. Its presence is therefore due to its partial solubility in the volume of ether used.

Primarily because of the low yield of the target compound in the crude product, but also because of the presence of unreacted dimethylphosphorochloridate which would make distillation (purification) difficult, and the uncertainty in the stability of the pyridyl product in an aqueous medium, no attempt was made to isolate the desired ester. Rather, as a result of the problems encountered in this system, we were encouraged to investigate an alternative route to the synthesis of the product (see 3.2.2 below).

3.2.2 SYNTHESIS INVOLVING 2,6-DIMETHYLPYRIDINE AS A BASE

We decided to follow a method reported by C.J. Lacey and L.M. Louw for the synthesis of choline alkyl phosphates.[9] Their method was immediately attractive as it held a number of chemical similarities to our own envisaged system, *viz.* in the initial step of the reaction, a chlorophosphate molecule is esterified in the presence of a nitrogen containing base. The chemistry is outlined in Scheme 3.1.

Scheme 3.1



The authors used 2,6-dimethylpyridine (pKa = 5.77)[35] quite successfully as the base and pentane (ether was found to be equally effective) as solvent, in the alkoxylation of methylphosphorodichloridate. They report that various combinations of other bases (triethylamine, pyridine or diisopropylethylamine) and other solvents (chloroform, methylene chloride, or acetonitrile) led to an intractable polymeric gum. We were therefore encouraged to use 2,6-dimethylpyridine as the external base to trap the hydrogen chloride generated during esterification. This base can be considered as a sterically hindered base so side reactions leading to demethylation of the phosphate ester group will be minimized.

A mixture of equimolar volumes of 2-pyridylmethanol and 2,6-dimethylpyridine were added dropwise to the ethereal solution of dimethyphosphorochloridate (a 20% excess mole ratio based on the mole ratio reported by Lacey and Louw was used) with cooling and stirring. There was an immediate fine, white precipitate. After

the reaction mixture had been stirred for 2 h at T ≤ 5°C, the precipitate was filtered off using a sintered glass filter and suction filtration, washed with freshly distilled dry cold ether and dried *in vacuo*. The ^{1}H NMR (D_2O) spectrum revealed that the salt is a mixture of 47% 2,6-dimethylpyridinium chloride and 53% protonated 2-pyridylmethanol.* There is no evidence for N-methyl bond formation. The solvent was removed from the filtrate *in vacuo*, leaving a clear oil. The ^{1}H NMR ($CDCl_3$) spectrum showed only 25% of the desired product (consistent with the yield of the white precipitate); unreacted 2-pyridylmethanol; 2,6-dimethylpyridine and dimethylphosphorochloridate. The result of this run can be summarized by the following equation (eq. 3.3). The procedure

$$\underline{S} + \underline{S}' \xrightarrow[T \leq 5°C,\ 2\ h]{\text{lutidine, } Et_2O} \underline{A} + \underline{SHCl}^{+\ -} + \text{lutidinium chloride} \qquad (3.3)$$

1 mole 1 mole 0.25 mole 0.13 mole 0.12 mole

*The proportion of the two pyridinium salts formed does not correspond to the basicity difference of 2,6-dimethylpyridine and 2-pyridylmethanol (pKa = 5.77 and 4.89, respectively). The pKa values relate, however, to the equilibrium situation in aqueous solution, while in our experiment, the two salts were formed by precipitating out of the etheral medium. It seems therefore that because of their low solubility, both salts separate out under non-equilibrium conditions and their proportion is determined by random protonation of one or the other nitrogen atom.

followed does not give especially promising results. The yield of the crude product was only 25% and cannot be favourably compared to a yield for compound 3.4, (R = propyl) in scheme 3.1 which after purification (distillation) was 67%. Presumably the lower yield of the former system can be attributed to the bifunctionality of the pyridyl substrate making it a more versatile and yet a less selective reagent. No attempt to optimize the conditions was considered worthwhile. Theoretically if the substrate, 2-pyridyl-methanol, competes with the external base for the hydrogen chloride liberated, then the reaction has a potential yield of only 50%. However, the full reaction potential was not reached and either way the problem of separating the product, the unreacted base and unreacted substrates (four components) still remained.

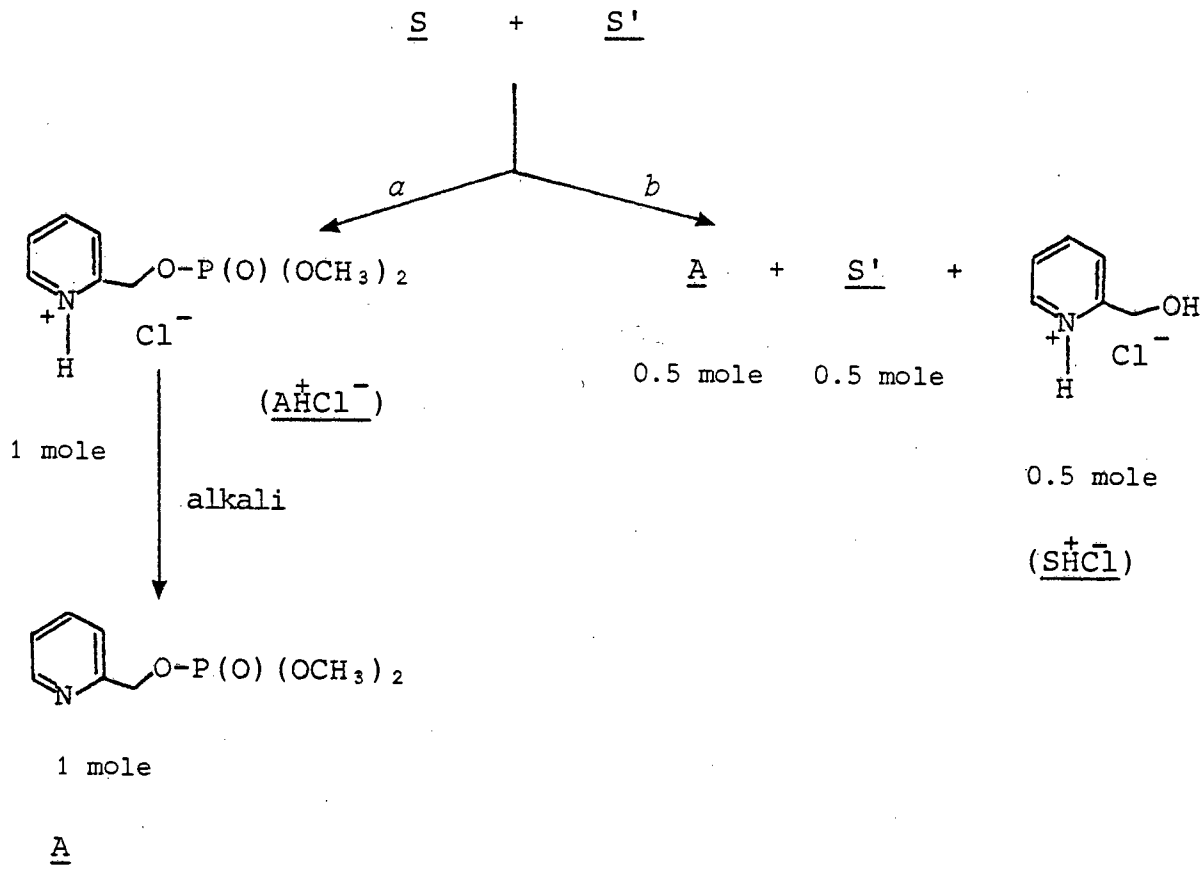
The idea of using an external base in the phosphorylation reaction was abandoned altogether in the hope that a system containing only the substrate alcohol (S) (to function both as the nucleophile and the base) and the phosphorylating agent may lead to a simpler synthetic procedure.

3.2.3 SYNTHESIS IN THE ABSENCE OF AN EXTERNAL BASE

The feasibility of the reaction (3.2) proceeding without an external base was thus investigated on the assumption that the reaction can proceed *via* either of the pathways illustrated in scheme 3.2 (pathway A or B). Initially the intermediate salt AH^+Cl^- was the target product. The dimethyl-(2-pyridylmethyl) phosphate A, can then be obtained from AH^+Cl^- after work up in an alkaline medium and extraction of the deprotonated species into an organic solvent.

The protonated salt $\underline{AH^+Cl^-}$ is presumably the more stable form of the product. The susceptibility of the pyridyl nitrogen in A to methylation is one of the topics under investigation in this chapter, so storing the product in the form of its conjugate acid may then be advisable.

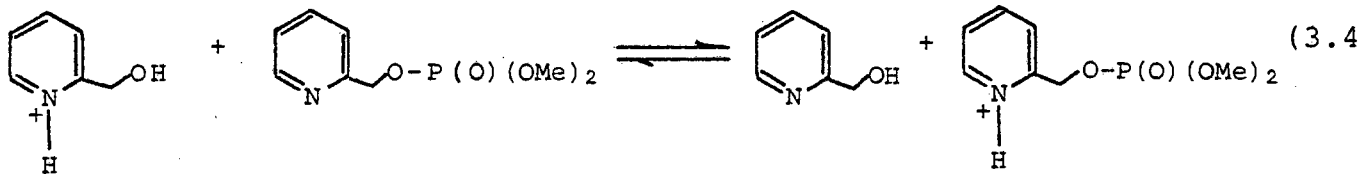
Scheme 3.2



Pathway *a* illustrates a direct route to the synthesis of the desired product, A. The necessary condition for its operation is that the basicity of the pyridyl nitrogen in the product is greater than that in the substrate (S), so that the hydrogen chloride liberated, could be trapped by the product. If pathway *a* were to operate we would get a precipitate in the reaction vessel and

once the reaction was complete, the solvent would be free of all components.

Pathway *b* shows the first step of the indirect route to the synthesis of A. Here the pKa of 2-pyridylmethanol must essentially be greater than the pKa of the product with the result that the hydrochloride salt of 2-pyridylmethanol ($\underline{SH^+Cl^-}$) precipitates out of solution. However, it can be expected that proton transfer can occur from one basic centre to another and that the following equilibrium (eq. 3.4) occurs and therefore completes pathway *b*.

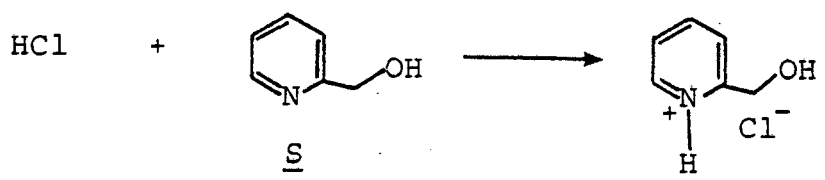


(3.4)

A 1:1 stoichrometric mixture of substrates will favour the equilibrium shifting in the forward direction as unreacted $(MeO)_2P(O)Cl$ will react with 2-pyridylmethanol as soon as it is released. This in effect removes the alcohol from the equilibrium reaction and according to Le Chatelier's principle the equilibrium will be shifted to the right hand side of the equation. If pathway *b* were to operate, an initial precipitate would also be formed. However, as the equilibrium is set up, the nature of the precipitate would change. It would be difficult to monitor this reaction without examining the precipitates. With the two extremes *a* and *b* as the only possible alternatives in mind, we set about to investigate the reaction.

The reaction was handled in a rigorously dry atmosphere inside a glove box with the aim of eliminating the possibility of chlorophosphate hydrolysis. This would not only directly decrease the substrate concentration (eq. 3.5) but also as hydrogen chloride formation proceeds, the 2-pyridylmethanol would become protonated (eq. 3.6) and this would therefore also decrease the concentration of the alcohol.

$$\underset{\underline{S'}}{(MeO)_2P(O)Cl} + H_2O \longrightarrow (MeO)_2P(O)(OH) + HCl \qquad (3.5)$$

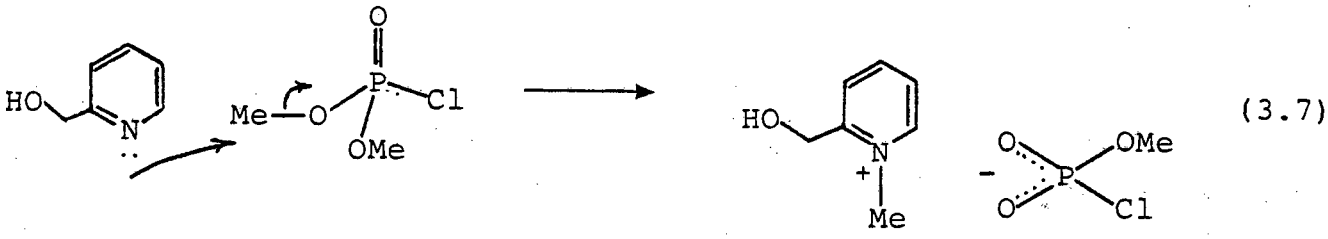


(3.6)

In addition to the above precautionary measure, 2-pyridylmethanol was distilled and stored over molecular sieves and dimethylphosphorochloridate and ether were distilled immediately prior to use. Great care was taken at all stages of the reaction to exclude moisture.

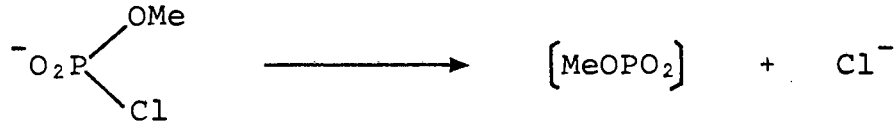
An equimolar etheral solution of dimethylphosphorochloridate and 2-pyridylmethanol was prepared with the immediate formation of a white precipitate. After 3.5 h the ethereal solution was separated from the white precipitate by decanting the solution into a second flask. After a further 19.5 h the ethereal solution was decanted into a third flask leaving a pink/white precipitate in flask two. 94 h after the reaction had been started a red syrup-like product had separated in flask three and the ethereal solution was once again removed into another flask (flask four). Finally, evaporation of the ether in flask four resulted in a thick red oil. The contents of all the flasks were examined by ^1H NMR spectroscopy.

From the ^{1}H NMR spectrum of the contents of flask one, it can be concluded that 88% of the product mixture consists of $\underline{SH^+Cl^-}$. The appearance of a singlet at δ4.55 in the ^{1}H NMR spectrum of the product mixture is identified as the N-methyl absorption of the [2-(N-methylpyridinium)] methanol ion. This accounts for 12% of the product mixture and indicates that under these reaction conditions, in addition to its function as a base, the pyridyl centre is functioning as a nucleophile which demethylates the phosphorylating agent (eq. 3.7). The absorption for the methylene protons of



(3.7)

the [2-(N-methylpyridinium)] methanol ion is masked by the absorption of the methylene protons of the protonated salt at δ4.90.[36] The intergration of the peak area for this singlet, the pyridyl protons and the N-methyl protons is consistent with that expected for the hydrogen atoms involved. There is no evidence for the presence of the counterion, $(MeO)P(O)(Cl)O^-$ in the first precipitate, and we believe that both the pyridinium and the N-methylpyridinium ions derived from the alcohol (S) exist as simple chloride salts. We have independent evidence[37] that anions such as that indicated in eq. 3.7 can spontaneously collapse yielding chloride anion and the metaphosphate-type species (eq. 3.8).



(3.8)

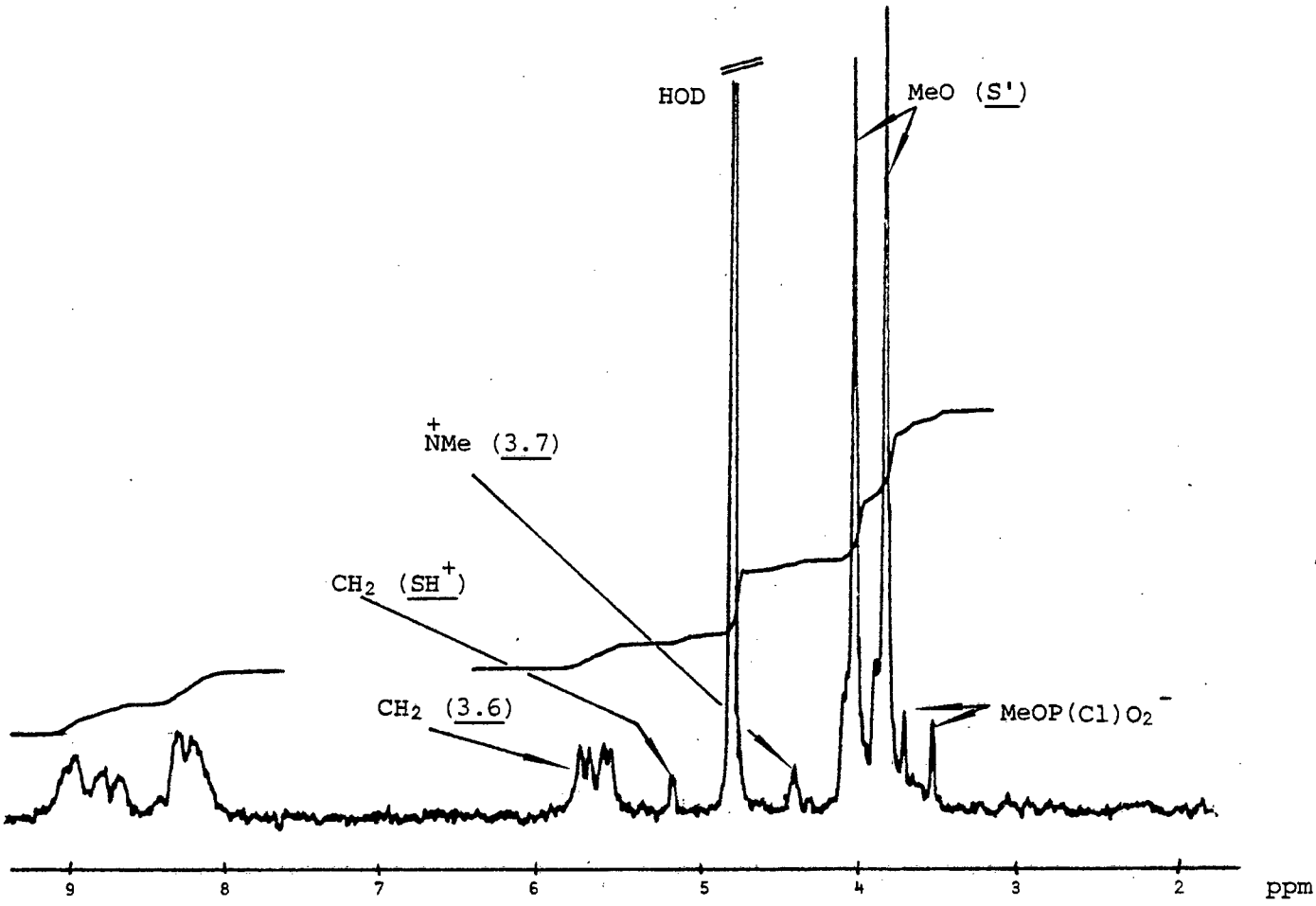
The white precipitate in fraction two was found by ^1H NMR spectroscopy to be a mixture of 78% $\underline{SH^+Cl^-}$ and 22% of the [2-(N-methylpyridinium)] methanol salt. The greater percentage of methylated 2-pyridylmethanol in fraction two compared with fraction one, is in keeping with the side reaction being slower than the primary reaction. The presence of a doublet (δ3.63) shifted upfield of the doublet for the methoxy protons of neutral $(MeO)_2P(O)Cl$ leads us to suspect that the counterion for the [2-(N-methylpyridinium)] methanol ion is in this case $^-O(MeO)P(O)Cl$. A shift upfield for the methoxy protons suggests a more shielded environment which would result if there was a negative charge on the molecule.

The formation of the hydrochloride salt of 2-pyridylmethanol as the major reaction product in fractions one and two is best explained in terms of the reaction proceeding *via* pathway *b*. In addition, a side reaction involving demethylation of the substrate accounts for 15 - 22% of the precipitated product mixture in these two fractions.

Analysis by ^1H NMR spectroscopy (D_2O) (fig. 3.1) of the viscous red oil which separated out of the ethereal solution in fraction three, reveals that P-O-CH_2 bond formation has been successful. Initially, due to the fact that there were two doublets of almost equal intensity, centered at δ5.62, it was assumed that two products

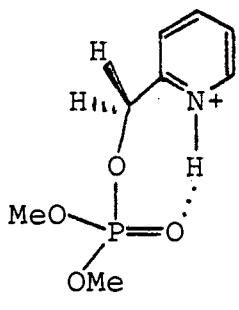
had formed in almost equal proportion (the chemical shift of these doublets indicates that the pyridyl nitrogen is charged).

Figure 3.1 ^{1}H NMR spectrum of contents of flask three



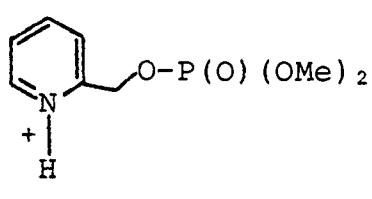
But a closer examination of the spectrum shows that the singlet at δ4.43 for a N-methylated product accounts for only 11% of the product mixture. Comparison with the ^{1}H NMR spectra obtained for fractions one and two confirms that this singlet is not due to methylated alcohol. We suspect that the methylene protons of the N-methylated product are masked by the doublet for the methylene protons of the protonated product - the major component. The splitting of the doublet at δ5.62 to a pair of doublets is postulated as being due to the unequivalency of the methylene protons.

The coupling constant $^{3}J_{H,P}$ = 8 Hz for both doublets. The coupling constant for the pure product A, synthesized in 3.2.4 is also 8 Hz. Perhaps a slowing down of the freedom of rotation within the P-O-C-C fragment on the ^{1}H NMR time scale, by a possible interaction of the pyridinium proton with the phosphoryl oxygen (structure 3.5) is the cause of this anomalous splitting.

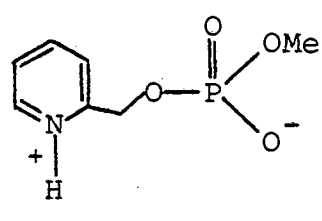


3.5

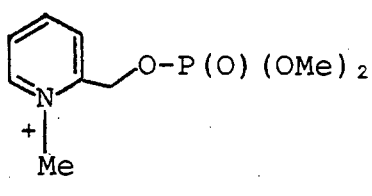
The two products containing the positively charged pyridyl nitrogen are postulated as containing either the cationic (3.6 and 3.7) or zwitterionic (3.8 and 3.9) structures.



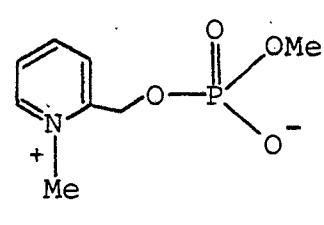
3.6



3.8

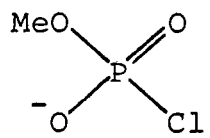


3.7

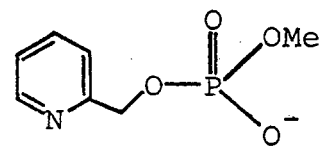


3.9

As further studies show that the oxygen → nitrogen methyl transfer in this group of compounds is slow, we believe that the cations 3.6 and 3.7 are the positively charged species present. The chloride ion is the anion more than likely corresponding to 3.6. Assignment of the anion corresponding to 3.7 is more difficult. Demethylation of both the substrate and the product can occur so the anion could be either 3.10 or 3.11.



3.10



3.11

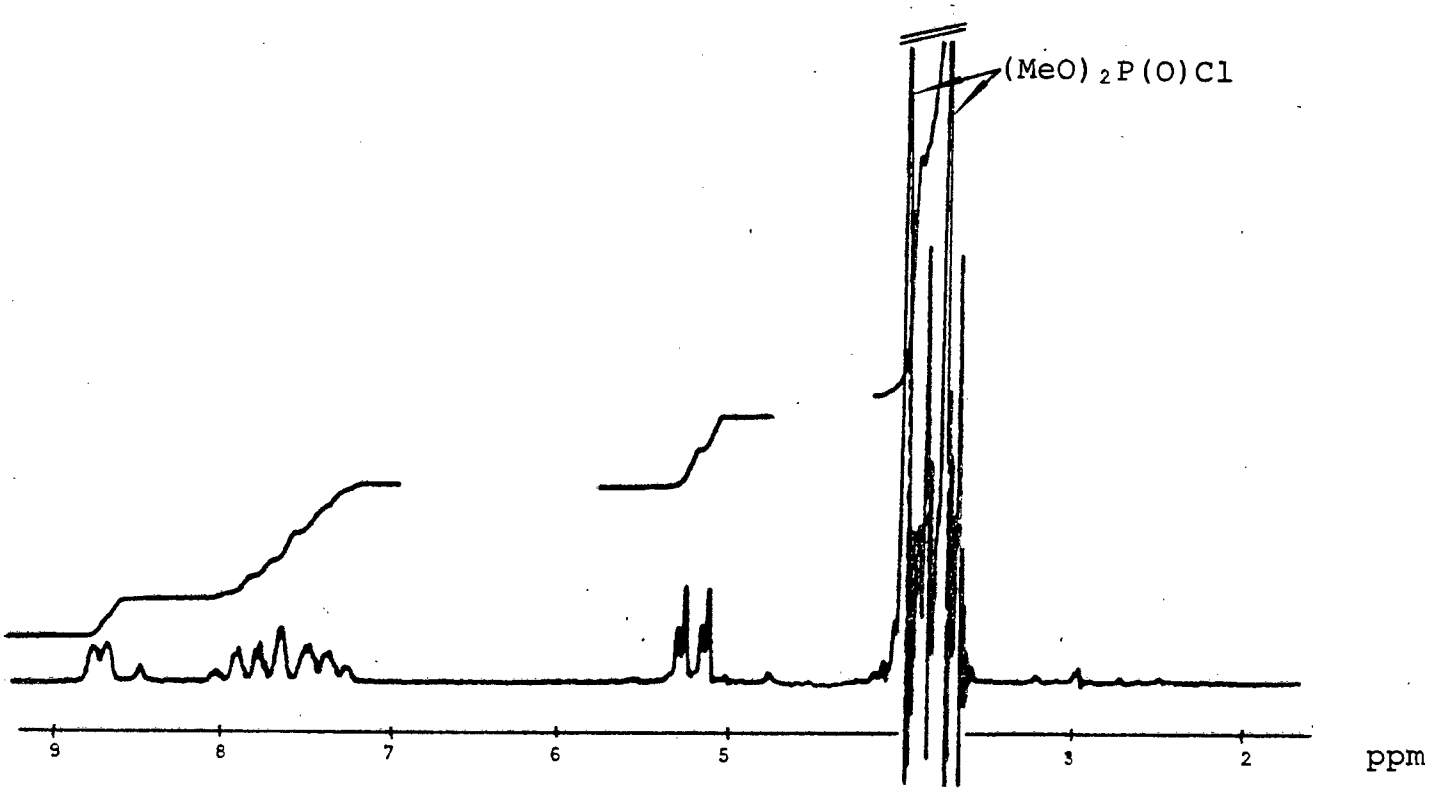
Evidence from ^{1}H NMR spectroscopy clearly shows a doublet upfield (δ3.63) of the doublet for neutral substrate $(MeO)_2P(O)Cl$. This doublet, assigned to the methyl ester group in the negatively charged phosphate corresponds in terms of its intensity to the signal at δ4.43 identified as the $\overset{+}{N}$-Me group. As the N-methylated salt was present to only approximately 11%, the intergration for the additional protons in the counterion 3.11 as compared to 3.10 could be within the limits of experimental error. This along with the fact that no further separation of the mixture was attempted does not permit a unique assignment to the counterion of 3.7.

However, because the electrophilicity of the methyl carbon in S' should be greater than that in the product A (as measured by the chemical shift of the methyl groups which are 3.93 and 3.83 respectively), and because the concentration of the chlorophosphate is greater than that of the product, we believe that the counterion is in fact 3.10. Nevertheless the important point to emerge from

the experiment is that the product can function as a nucleophile and so besides disturbing the stoichiometry of the reaction, this certainly makes the system more complicated.

Analysis of the ^1H NMR spectrum of the contents of flask four (fig. 3.2) reveals that unreacted dimethylphosphorochloridate is present - 65 mole %. More important than this is the presence of the doublet (again it is split to a pair of doublets) at δ5.25 indicative of product formation (25 mole %).

Figure 3.2 H NMR spectrum of contents of flask four



Due to our uncertainty of the stability of the target compound, the contents of flask four were analyzed by ^1H NMR after various time intervals. (The ^1H NMR tube was kept sealed at room temperature during this time.) After 24 h (fig. 3.3) a singlet at δ3.00 was observed. It is obvious that this absorption increases at the expense of the doublet at δ3.93 (unreacted $(MeO)_2P(O)Cl$ fig.

3.4). This new signal is assigned to methyl chloride. (The literature chemical shift of methyl chloride at δ3.05 supports our assignment.) The formation of methyl chloride under the given reaction conditions is best explained in terms of an S_N2 type nucleophilic displacement reaction of chloride ion at methyl carbon. The formation of chloride ion is shown by eq. 3.8. The nucleophilic attack of this ion at dimethylphosphorochloridate (eq. 3.9) yields a molecule of methyl chloride and an anion, which, according to eq. 3.8 is capable of regenerating chloride ion, thus requiring only catalytic amounts of this ion to promote the observed changes. Obvious by its absence is the absorption at δ3.00 in fig. 3.5.

(3.9)

This ^1H NMR spectrum was recorded after removal under vacuum of any volatile products formed in the NMR tube. Methyl chloride is a gas (b.p. 24°C) and this spectrum satisfies us that indeed our assignment is correct. This side reaction is, of course, not possible once contamination by ionic chloride has been removed and its observation merely serves to illustrate the importance of attention been given to good filtration technique, maintaining a cold reaction medium and keeping the time between crude product isolation and purification at a minimum.

Figure 3.3

T = 24 h

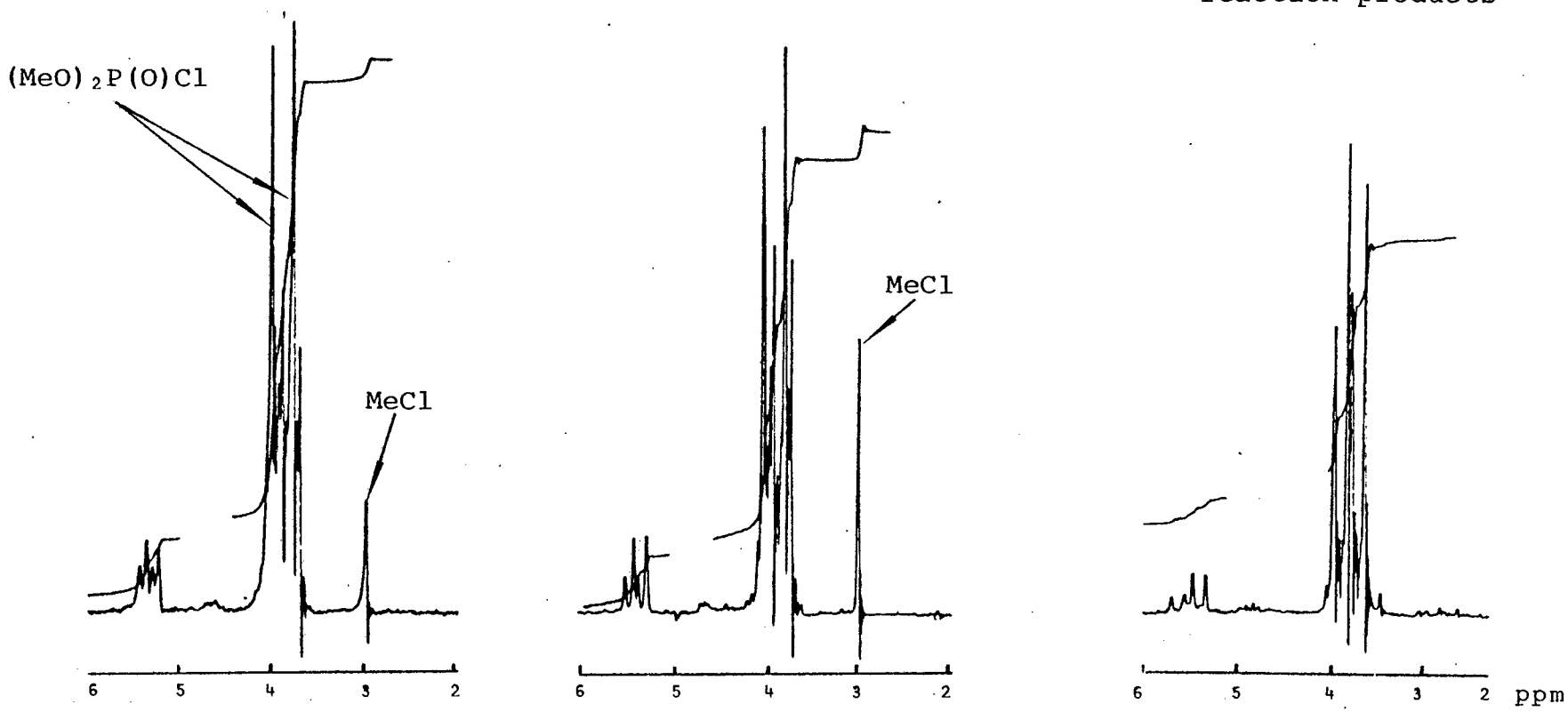
Figure 3.4

T = 48 h

Figure 3.5

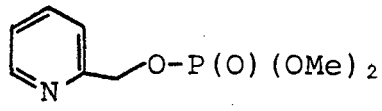
T = 72 h

After removal of volatile reaction products

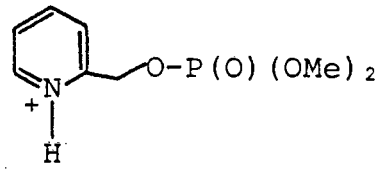


^{1}H NMR analysis of the contents of flask 4 after various time intervals

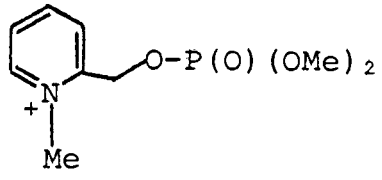
Although the product A was not independently isolated and characterized at this stage, its formation is unambiguous. The total yield of the phosphorylation products (calculated from analysis of the mole proportions of compounds in the ^1H NMR spectra of the contents of flask three and four) is estimated as follows:



24%



19%



3%

These values are consistent with the recovery of the hydrochloride salt of 2-pyridylmethanol from flasks one and two.

Before reaching a conclusion about this experiment, it must be remembered that removal of the precipitated hydrochloride salt of 2-pyridylmethanol (in flasks one and two) eliminates any possibility for the equilibrium represented by eq. 3.4 being established. However, the fact that this salt was isolated is evidence for the reaction proceeding via pathway *b* initially. Later (from flask three) we get evidence for $\underline{AH^+Cl^-}$ formation which illustrates that pathway *a* is by no means a trivial alternative reaction pathway. Two factors are obviously in play. Firstly, basicity. We believe the basicity of 2-pyridylmethanol will be greater than that in the phosphorylation product due to the electron withdrawing effect

of the phosphoryl group. Secondly, concentration effects are important. As the reaction proceeds, more of the product is formed and less of the alcohol remains. So inspite of the lower basicity of the product, it is present in a greater concentration than the alcohol and may function as a more effective base. Clearly the initial condensation reaction is relatively slow at ambident temperature. Any attempt to increase the rate of reaction may enhance the nucleophilicity of the pyridyl nitrogen in the alcohol and/or product and this would lead to a greater chance of demethylation. Methyl chloride formation may also increase, especially if the reaction was carried out in one reaction vessel whereby nucleophilic chloride ion was always present.

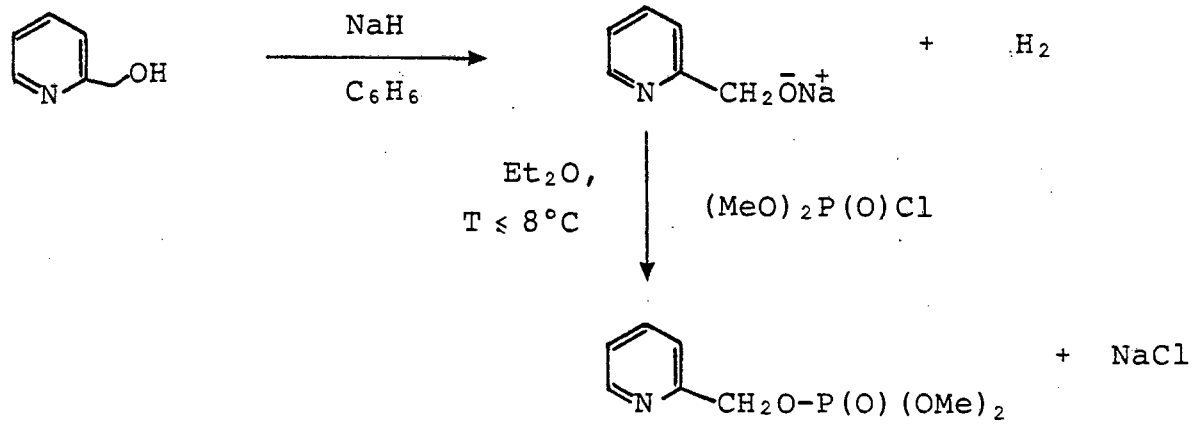
This experiment illustrates that 2-pyridylmethanol functions not only as a primary reagent but also as an effective base (and to a lesser extent a demethylating agent). The product also exhibits basic and nucleophilic properties. As basicity and nucleophilicity more often than not run parallel, it would be difficult to utilize the pyridyl nitrogen centre (either in the alcohol and/or product) without its concurrent function as a nucleophile. Nevertheless we were convinced that there existed a synthetic route in which we could recover the product more quantitatively. This is described in 3.2.4 below.

3.2.4 THE "ALKOXIDE ION METHOD"

Significant reactivity enhancement of alcohols can be achieved by converting the alcohol into its conjugate base. In fact the success of the second alkoxylation in the method described by Lacey and

Louw (scheme 3.1) in the synthesis of alkyl (2-dimethylamino)ethyl-methyl phosphates, is ascribed to the preference of the alkoxide ion for the hard acid centre such as the phosphorus atom of the phosphoryl group.[40] Particularly since no appreciable demethylation was reported, we were encouraged to attempt to enhance the nucleophilicity of the oxygen atom of the alcohol function, prior to the phosphorylation reaction. The proposed reaction scheme is illustrated in scheme 3.3

Scheme 3.3



The reaction was carried out under nitrogen using benzene and ether as solvents. Sodium hydride was chosen as a base and sodium chloride precipitated out of solution during the reaction. This procedure does not involve hydrogen chloride formation and therefore it has the added advantage of not requiring the utilization of a base to effect the trapping of the acidic by-product. The phosphorylation relies on the formation of the sodium salt of the alcohol. This salt was siphoned under a positive nitrogen pressure, from the slight excess of sodium hydride used in its preparation, the sodium hydride washed with benzene (3 x 30 ml aliquots) and

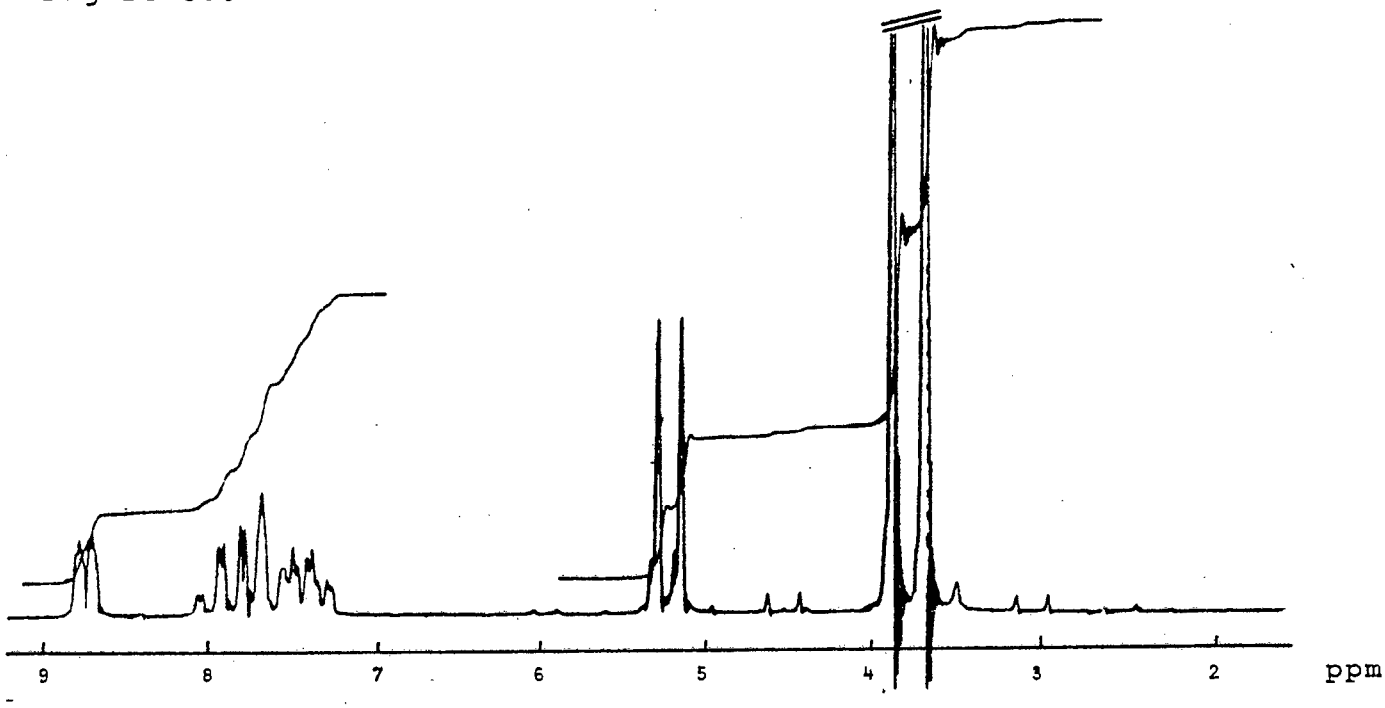
the combined benzene solution added dropwise to an ice-bath cooled solution of dimethylphosphorochloridate in ether. The temperature was maintained at less or equal to 8°C throughout the addition. After stirring for 1.5 h, the precipitated sodium chloride was filtered using gravity filtration and washed with fresh solvent. Evaporation of the combined supernatant and washings provided a red oil contaminated with a fine, white precipitate. The ^{1}H NMR spectrum of this product showed a doublet at δ5.25 which confirms the formation of the P-O-CH_2 bond. There is a trace of unreacted $(MeO)_2P(O)Cl$ and a singlet at δ4.90 which is assigned to protonated 2-pyridylmethanol. The formation of this salt may have been due to the introduction of water with one of the reagents used in the synthesis. This would lead to some hydrolysis of dimethylphosphorochloridate as was shown in eq. 3.5 and 3.6. However, as the crude yield of the target compound was 78% (calculated from ^{1}H NMR data), the presence of this salt which could be easily removed by column chromatography was not of too much concern.

We were particularly interested in the chemical shift range δ4.00 - δ4.80 - the lower and upper limits of $\underline{N}^+$-methyl ammonium group. The stability of the desired product was unknown to us at this time and we were anxious to know if the intramolecular rearrangement (eq. 3.1, $\sim$ = CH_2), would occur. Absence of absorption in this range, in the spectrum of the crude product from the synthesis was indication that product A was not rearranging intramolecularly or reacting intermolecularly under these conditions. We were also interested in the possibility of the demethylation of the methylphosphate group by the 2-pyridylmethoxide ion, which would yield (2-pyridylmethyl)methyl ether. No signal at δ *ca.* 3.3,

corresponding to a methyl ether function, MeOR could, however, be detected in the ^1H NMR spectrum of the mixture.

The crude phosphate was purified on a silica gel column using a chloroform : ethanol (4:1) solvent system and the purity of the phosphate was confirmed by TLC, ^1H NMR, elemental and mass spectral analysis. The ^1H NMR spectrum of the purified dimethyl-(2-pyridyl-methyl) phosphate is presented in fig. 3.6.

Figure 3.6



When the above preparation was repeated with strict attention being paid to the exclusion of water, both from the reagents and solvents $(MeO)_2P(O)Cl$ was distilled the very day it was to be used, benzene was dried over pressed sodium wire, ether was refluxed for 0.5 h over sodium hydride before being collected, no $C_6H_7O\overset{+}{N}HCl^-$ was identified in the ^1H NMR spectrum of the product. The reaction mixture was also stirred for an additional 1.5 h. This gave a crude yield of product of 86% and the yield after column chromatography was 79%. The precipitated sodium chloride was in both cases found to be contaminated by the pyridylmethyl phosphate product.

In solution, the salt appeared as a fine, white precipitate, but attempts to separate it were not wholly satisfactory. Filtering by gravity filtration, filtering by suction filtration and centrifugation were tried, and in each method the precipitate was washed well with freshly distilled solvent. However, in none of these cases was a pure, white salt obtained and this would account for the less than 100% yield of the product.

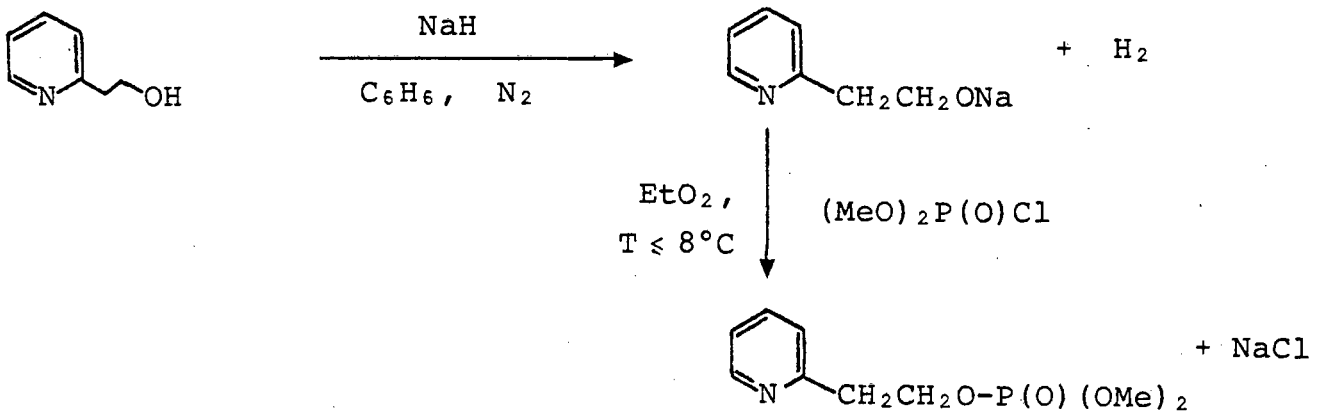
As was already mentioned, the mass spectrum of A was recorded and provided additional confirmation of its structure. This is discussed in ch. 7.

3.3 SYNTHESIS OF DIMETHYL-[β-(2-PYRIDYLETHYL)] PHOSPHATE, (B)

Since it was evident that β-(2-pyridyl)-ethanol can compete with amines such as triethylamine and 2,6-dimethyl pyridine as a basic centre, no attempts to repeat 3.2.1, 3.2.2 and 3.2.3 with this substrate in lieu of 2-pyridylmethanol were undertaken. Instead the method described in 3.2.4 for the synthesis of dimethyl-(2-pyridylmethyl) phosphate was followed as it has proved successful.

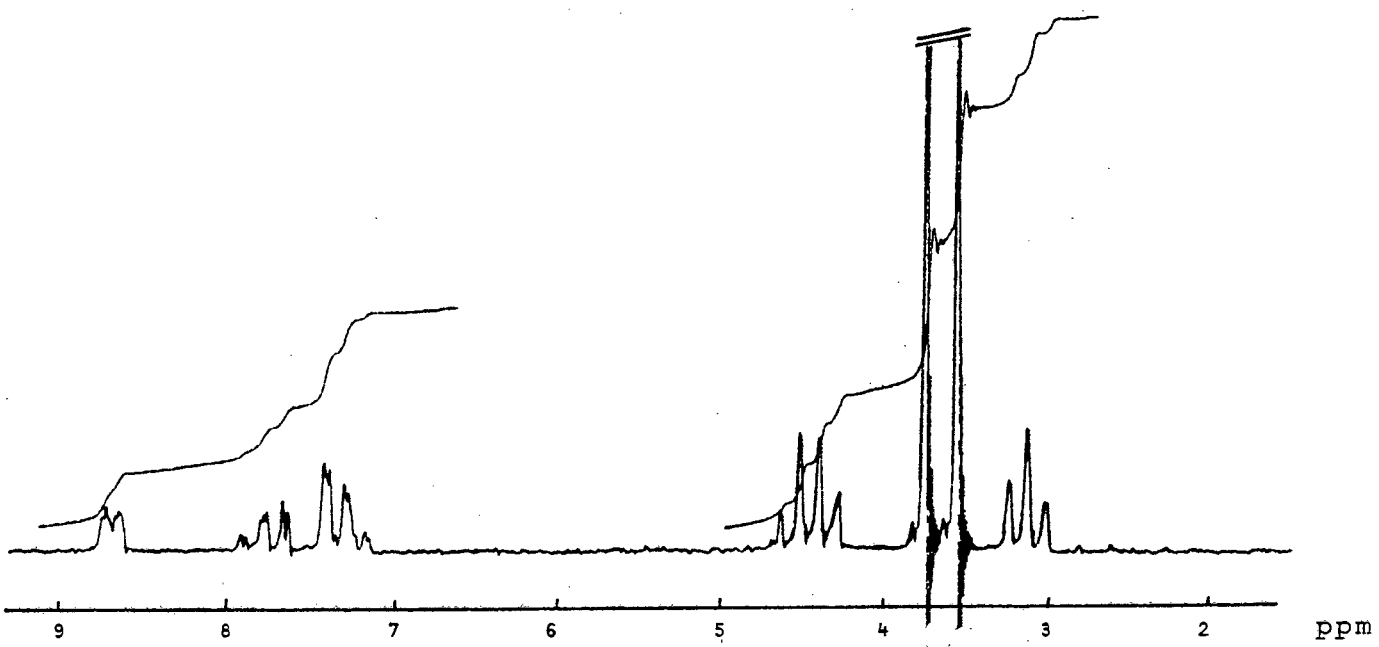
Once again the alkoxylation proceeds by attack of the "hard" basic oxygen on the "hard" phosphorus acid centre with expulsion of the chloride ion to form sodium chloride. The product was purified by column chromatography (yield = 76%) and identified by ^{1}H NMR, elemental and mass spectral analysis. The reaction is illustrated in scheme 3.4.

Scheme 3.4



The ^1H NMR spectrum of the purified dimethyl-[β-(2-pyridylethyl)] phosphate is presented in fig. 3.7.

Figure 3.7



The most characteristic feature of the ^1H NMR spectrum for structural assignment is the presence of a 2H quartet at δ4.47, $^3J_{H,P}$ = 7 Hz. This is the absorption for the methylene protons of the phosphate, β with respect to the pyridine ring. Since phosphorylation of the alcohol indroduces additional spin-spin coupling due

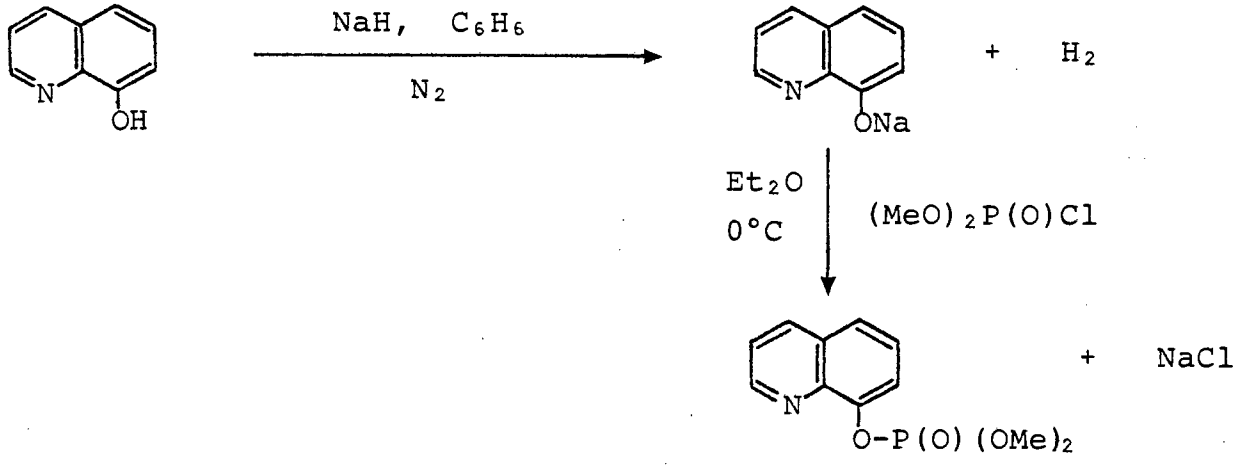
to the ^{31}P nucleus, the methylene group signal should correspond to an A_2B system. Such a system would be expected to give a doublet of triplets pattern; however, in the case of the $P(O)O\underline{CH_2}CH_2$ group, the values of $J_{H,H}$ and $J_{H,P}$ are approximately equal (7 Hz) and the methylene signal is reduced to a quartet corresponding to an A_3 system. The observed intergration fits closely to the expected ratio of the hydrogen atoms involved.

The mass spectrum of the product confirms its structure and information pertaining to its fragmentation pathways is contained in ch. 7.

3.4 SYNTHESIS OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE, (C)

The "alkoxide ion method" for the synthesis of the aforementioned compounds was found to be the most favourable and it was also successfully used for the synthesis of dimethyl-(quinolin-8-yl) phosphate. As with the other phosphorylations described earlier by this method (3.2.4 and 3.3.1) the esterification of dimethyl-phosphorochloridate by 8-hydroxyquinoline resulted from nucleophilic attack at the phosphorus centre by the phenoxide ion. Scheme 3.5 illustrates the reaction.

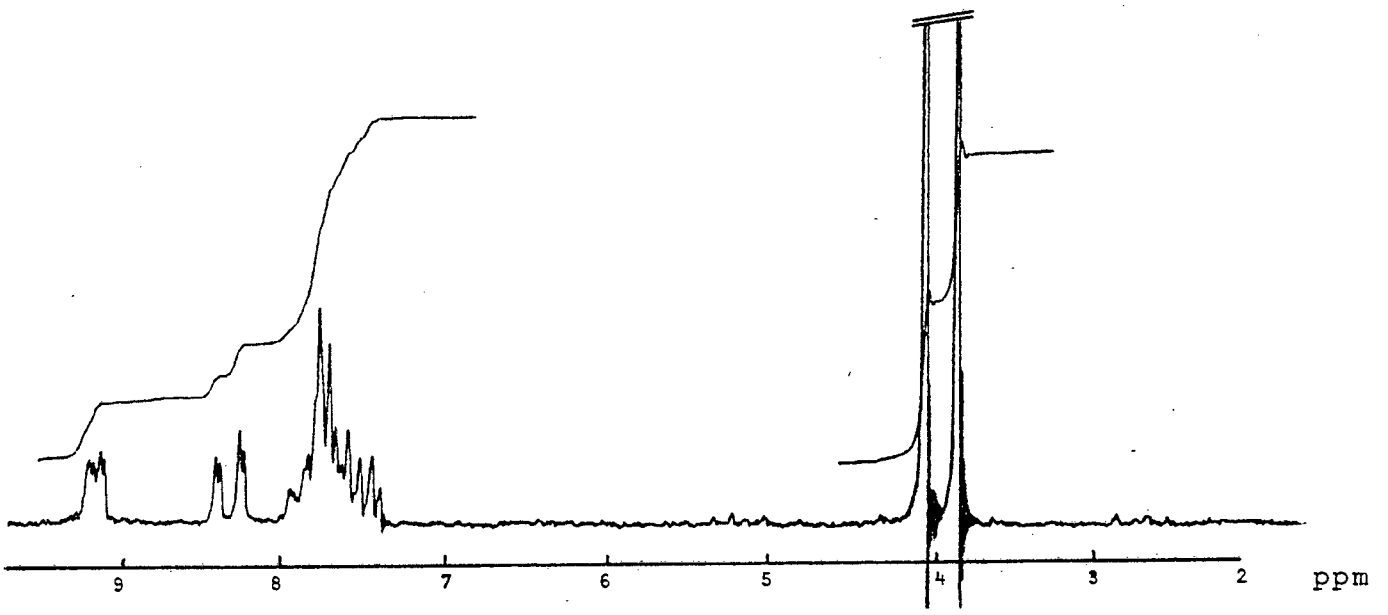
Scheme 3.5



The dimethyl-(quinolin-8-yl) phosphate was obtained as pale yellow crystals in 75% yield and as these gave a satisfactory elemental analysis and a sharp melting point, no further purification was needed. The crystals were also characterized by ^{1}H NMR and mass spectral analysis (see ch. 7). The ^{1}H NMR spectrum ($CDCl_3$) of the product (fig. 3.8) confirms the successful phosphorylation of 8-hydroxyquinoline. There is a pronounced shift downfield for the proton *ortho* to the quinolyl nitrogen and the doublet of doublets shifts from δ8.78 in the free phenol to δ9.1 ($\Delta\delta$0.32) in the phosphorylated phenol. This significant change in chemical shift is attributed to the electron withdrawal by the phosphoryloxy substituent relative to that of the free OH group. Interestingly enough, the effect of this structural change on the chemical shift of the hydrogen at position 7 in the quinolyl ring is much weaker ($\Delta\delta$0.10). This could suggest some intramolecular donor-acceptor interactions between the nitrogen atom and the electrophilic phosphorus centre, selectively decreasing electron density at position 1 (hence, at position 2) of the ring. Such types of intramolecular

interactions occurring in the solid state have recently been reported[41] for phosphate esters derived from 8-hydroxyquinoline.

Figure 3.8



The quinolyl substituent exerts a more pronounced electron withdrawing effect on the O-CH_3 groups than the 2-pyridylmethyl and 2-pyridylethyl analogues and this effect can be observed in the chemical shift of the O-CH_3 absorption for the three esters. The O-CH_3 proton resonance ($CDCl_3$) occurs at δ4.07 for compound C as compared to δ3.83 and δ3.75 for compound A and B respectively. The small shift upfield ($\Delta\delta$0.08) noted for the O-CH_3 resonance in B is directly attributable to the additional methylene link in the pyridylalkyl substituent which by lengthening the carbon backbone through which the electron withdrawing effect of the pyridyl group is transmitted, so reduces this effect. In fact the chemical shift of the O-CH_3 absorption in C is almost identical to that observed for trimethyl phosphate δ3.76 (CCl_4).[42]

3.5 SYNTHESIS OF DIMETHYL-(4-PYRIDYLMETHYL) PHOSPHATE, (D)

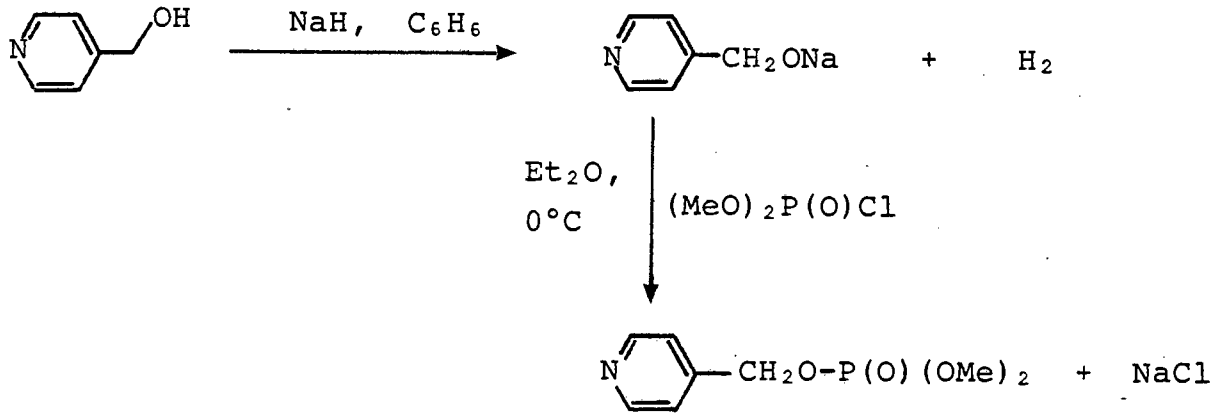
Although it is evident that the "alkoxide" method as described in 3.2.4, 3.3.1 and 3.4.1, offers a satisfactory preparative route to the synthesis of the dimethylalkyl phosphates containing a nitrogen heterocyclic substituent in the ester group, the possible participation of complicating side reactions which would arise primarily from the nucleophilicity of the pyridyl nitrogen and would be dependent on the steric environment at this nitrogen atom, would more than likely be dominant in the 4-pyridylmethyl derivative compared to the analogues A, B and C which are more sterically crowded at the pyridyl centre. We were particularly interested in synthesizing the target compound D in order to be able to compare its behaviour to the 2-pyridylmethyl isomer, A.

3.5.1

The first problem to overcome in this synthesis was the purification of 4-pyridylmethanol. In view of a literature report[43] whereby benzene was found to be a favourable solvent in which recrystallization of 4-pyridylmethanol could be effected, we attempted to purify the substrate. However, contrary to this report, numerous attempts at this recrystallization failed. Indeed efforts to recrystallize the substrate using various other solvents were also unsuccessful. After a further search of the literature,[44] we resorted to purifying 4-pyridylmethanol by distillating it (120°C/ 0.2 mm Hg) and then recrystallizing it from benzene. A product of satisfactory purity was obtained (mp 58-61°C, lit.[43] mp 57.8 - 58.8), however, the yield of this product was low (45%).

The procedure followed was effectively the same as that described in 3.2.4 and is illustrated in scheme 3.6.

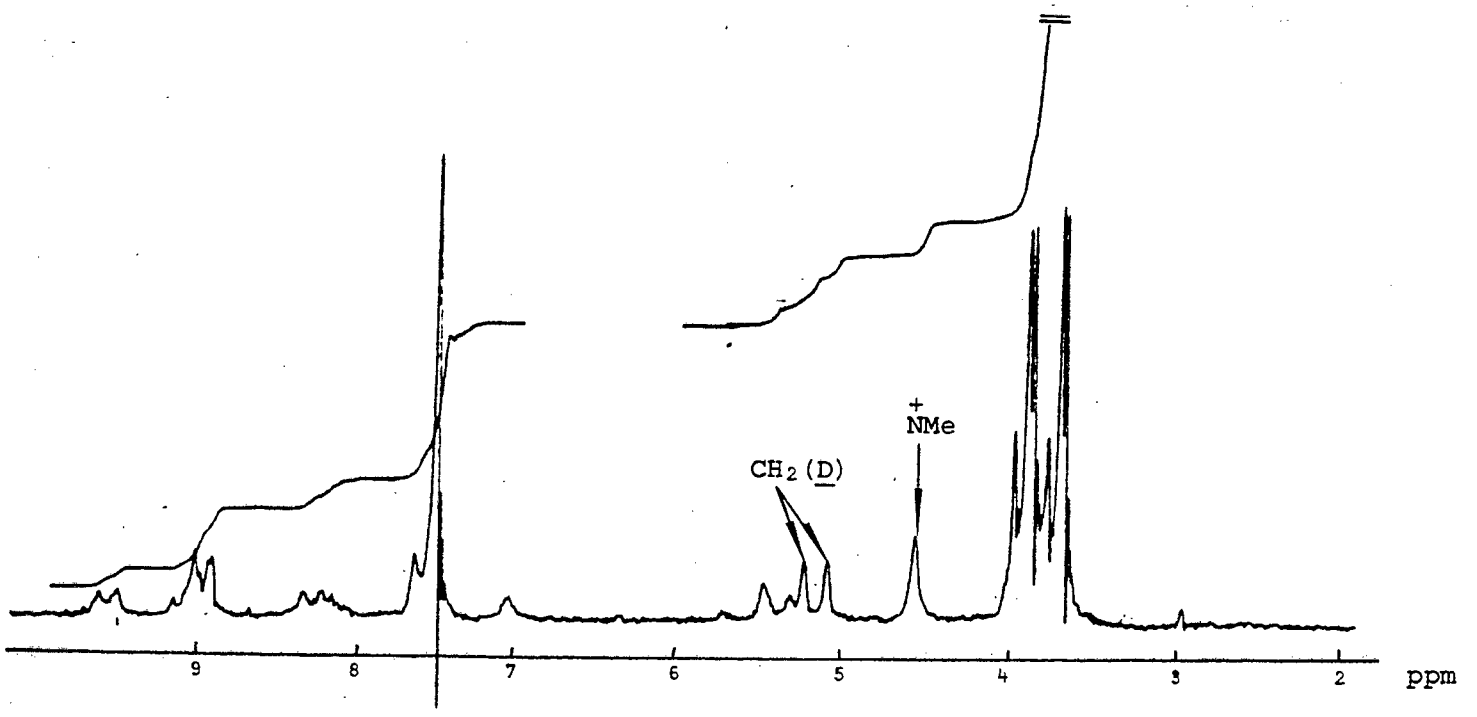
Scheme 3.6



D

The crude product mixture was found by ^1H NMR spectroscopy (fig. 3.9) to contain the target compound D as well as the N-methylated salt of dimethyl-(4-pyridylmethyl) phosphate in a molar ratio 2:1.

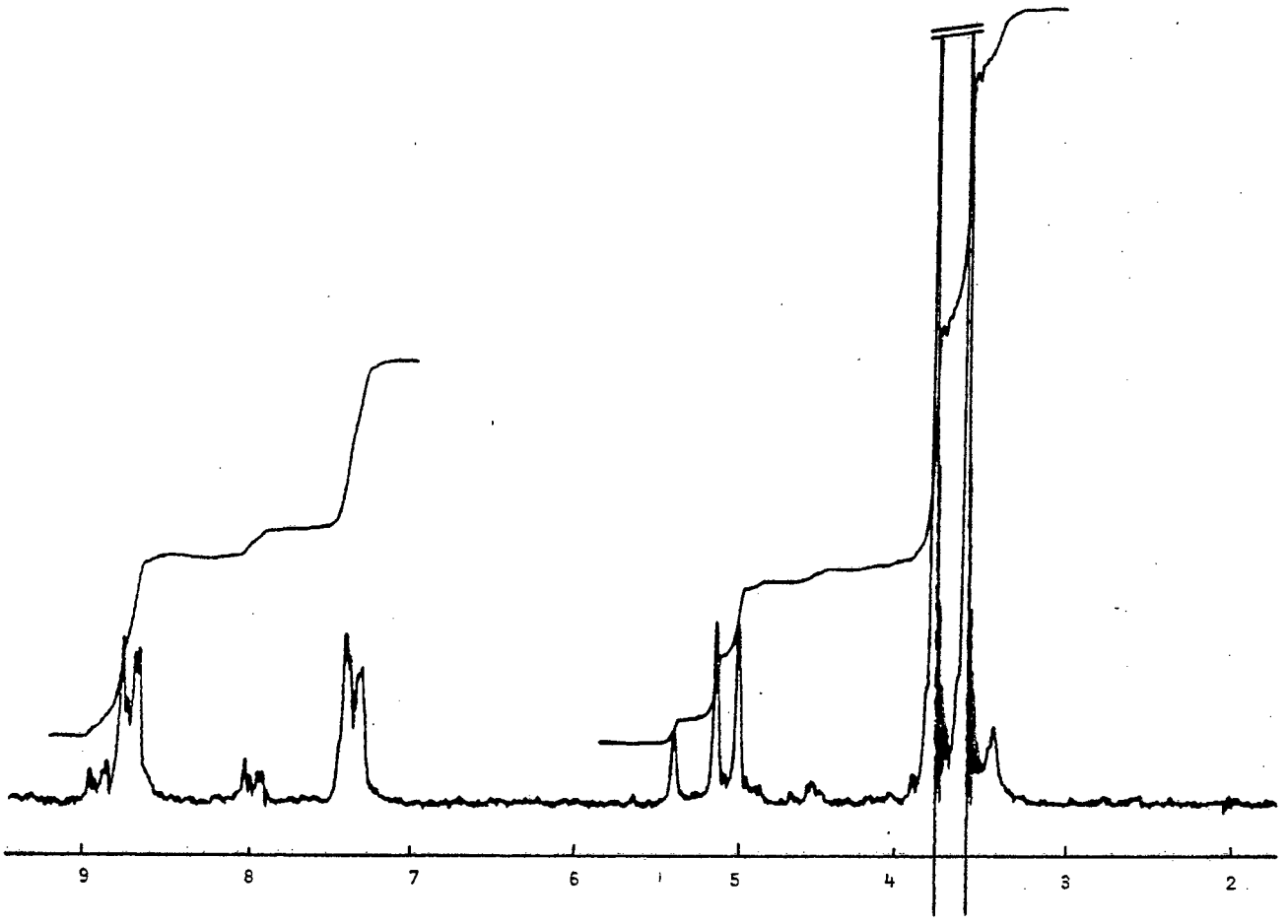
Figure 3.9



A characteristic feature of the NMR spectrum of dimethyl-(4-pyridylmethylphosphate is the doublet at δ5.16, ($J_{H,P}$ = 8 Hz), assigned to the methylene group, and split to a doublet because of the spin-spin coupling to the ^{31}P nucleus. The singlet at δ4.58 in fig. 3.9, characteristic for the N-methyl pyridinium group is evidence for the O→N methyl migration. This transfer occurs most likely via an intermolecular mechanism and it indeed contrasts with the behaviour of the 2-pyridylmethyl isomer which showed no evidence for the N-methyl absorption during its preparation. Shifted slightly downfield of the doublet for the methylene protons of the neutral product is a doublet centered at δ5.40, and this is assigned to the methylene protons of the N-methylated salt of the product.

The first attempt to purify the product by column chromatography was not all together successful. The red oil obtained was identified by ^{1}H NMR spectroscopy (fig. 3.10) and found to contain dimethyl-(4-pyridylmethyl) phosphate and the hydrochloride salt of 4-pyridylmethanol in a ratio of 6:1. The singlet at δ5.42 in this spectrum is assigned to the methylene protons of the protonated alcohol. This shift downfield, Δδ0.69, from δ4.73 for the methylene absorption in the neutral alcohol, is in line with positive charge development on the nitrogen atom causing the protons to become more deshielded. Observation of this salt in fig. 3.9 was less noticeable as the spectral absorptions overlap with those of the N-methylated salt of dimethyl-(4-pyridylmethyl) phosphate.

Figure 3.10



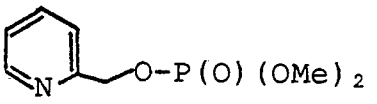
In the second attempt to purify the product, more attention was given to the chromatographic technique employed, and finally this afforded the pure product. The most noticeable feature of the ^{1}H NMR spectrum of dimethyl-(4-pyridylmethyl) phosphate compared to that of the 2-pyridylmethyl derivative, is the pattern of the pyridyl proton absorptions. The para-substituted pyridine ring results in a characteristic pair of doublet of doublets of equal intensity - the lower field dd being due to the protons α to the pyridyl nitrogen. The OCH_3 absorption is as expected, very near to that observed for dimethyl-(2-pyridylmethyl) phosphate - δ3.82 vs. δ3.83 respectively. However, the methylene proton absorption is upfield ($\Delta\delta$0.09) of the doublet for the same absorption in the 2-pyridylmethyl analogue, most likely the result of the more remote location of the electronegative ring nitrogen atom.

Chapter 4

Reactivity of Dimethyl (arylalkyl) Phosphates

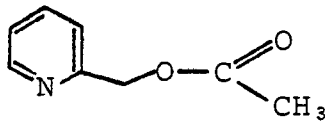
4.1 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE, A

4.1.1 INTRODUCTION

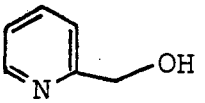


A

Having successfully developed a route to the synthesis of the title compound, we were then in a position to study its chemical reactivity. This was investigated from two directions. Firstly, compound A was refluxed in various solvents (selected for their differing properties) with a view to obtaining an insight into the importance of the intrinsic properties of the solvent, to the overall reactivity of the chemical system. And, secondly, the reactivity of compound A in water was compared to the reactivity of its acetyl analogue, compound E, and to its parent alcohol, S, both with trimethyl phosphate (TMP) in water.



E



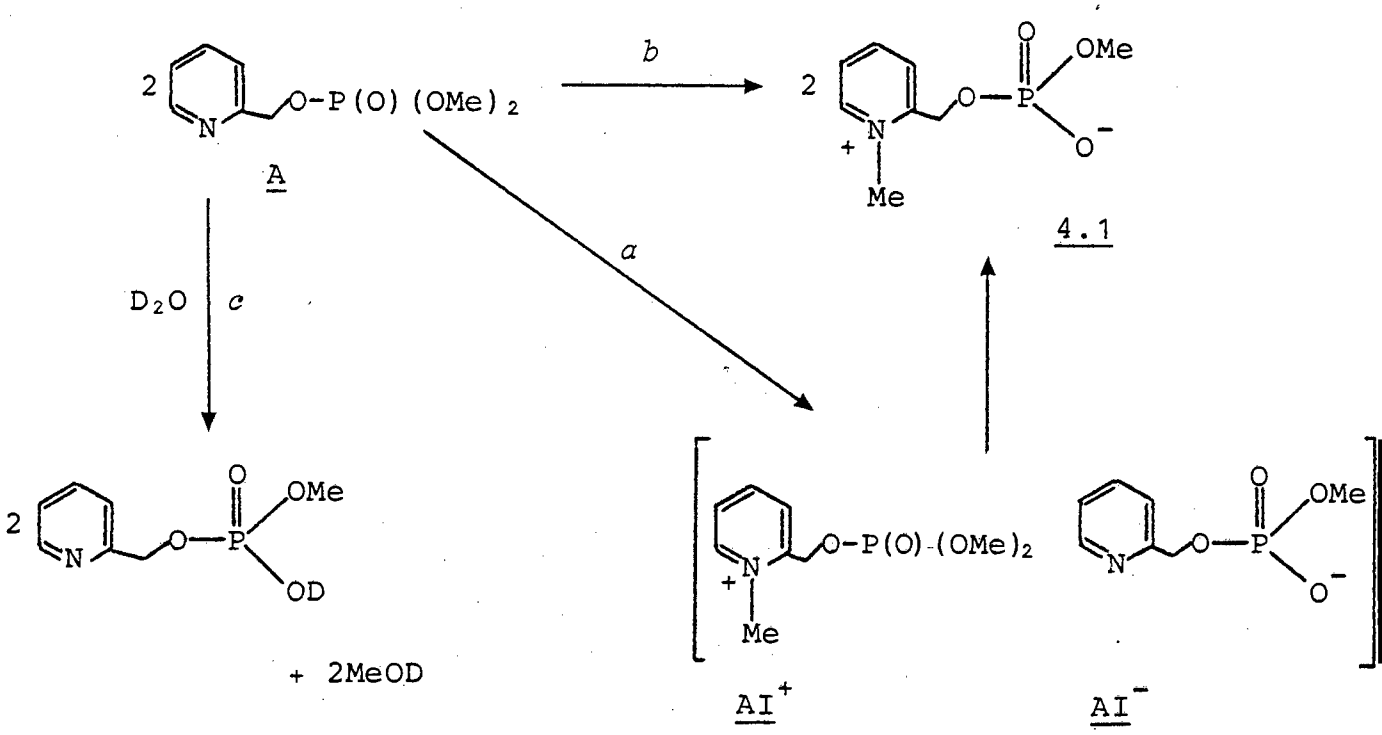
S

Acetate E was introduced to this study for the following reasons. Since the electronic effects of the acetoxy and dialkylphosphoryloxy groups are similar (σ_I values are 0.46 and 0.58, respectively[45]), the nucleophilicity of the pyridine nitrogen in A and E should not

be much different. The comparison of the reactivity of E with respect to (obviously) an external methylating agent (TMP) with that of the "self-methylating" reactivity of A could shed some light on the importance of the intramolecular pathway of methylation, available for the latter substrate. The reactivity of the parent alcohol S was expected to serve as a reference for a system in which any polar (and steric) effects of an acyl group are absent.

^{1}H NMR spectroscopy is a convenient analytical procedure for monitoring the anticipated oxygen to nitrogen methyl transfer. This technique seems to be ideal for this type of chemical change, since the reaction involves replacement of the methyl phosphate signal (*ca.* δ3.9, d, $^3J_{H,P}$ = 11 Hz), by another signal (*ca.* δ4.5, s) assigned to the N-methyl pyridinium group. The reaction can proceed intermolecularly (pathway *a*) or intramolecularly (pathway *b*) - see scheme 4.1. Both processes would be expected eventually to give rise to the zwitterionic structure 4.1. The possible reaction involving the hydrolysis of the methyl ester function is indicated in scheme 4.1 by pathway *c*.

Scheme 4.1



4.1.2 RESULTS

The solvents chosen for this study were chloroform (an apolar aprotic solvent), acetone (a dipolar aprotic solvent), acetonitrile (a dipolar aprotic solvent), dimethyl sulfoxide (a dipolar aprotic solvent) and water (a polar protic solvent). Because of the technique employed, the deuterated forms of the solvents were used.

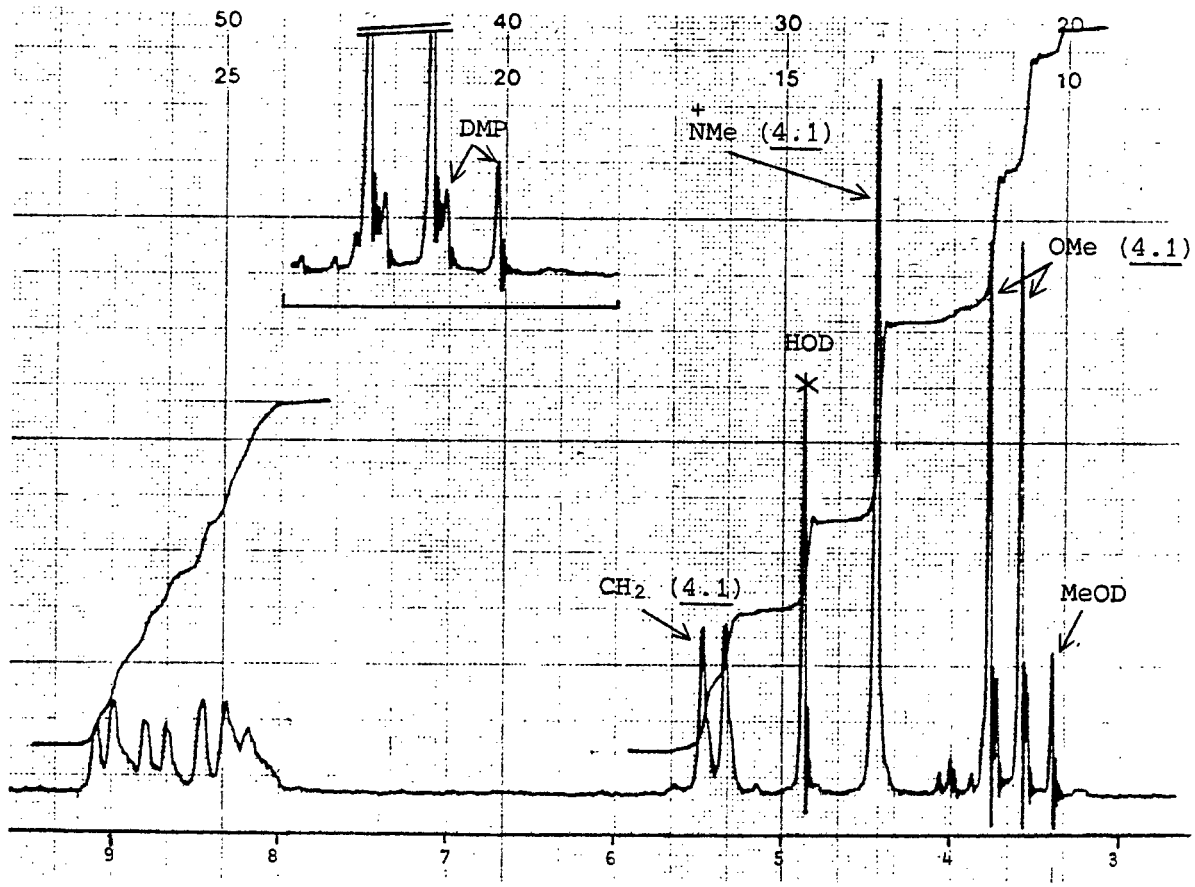
Compound A was refluxed in $CDCl_3$ (6 h), $CD_3C(O)CD_3$ (12 h) and CD_3CN (18 h) and there was no indication of methyl group transfer. Similarly no O→N methyl transfer was observed in a DMSO-d_6 solution of the substrate, maintained at room temperature (*ca.* 23°C) for 52 days. Studies of compound A in the absence of solvent at room temperature (*ca.* 23°C) for 4 months, and at 10°C (in a

refrigerator at *ca.* 8°C) over a period of 14 months, reveal that the methyl phosphotriester linkages are stable to the pyridyl nitrogen. The low reactivity of A contrasts with that of the β-(dimethylamino)ethyl analoque in which the isomerisation was complete after 28 days at 20°C.[9] Since the Swain-Scott parameters n, for triethylamine and 2-picoline differ by only 0.34 unit,[46] the difference in reactivity of A and the β-(dimethylamino)-ethyl substrate, results probably from the steric hindrance offered by the bulky 2-(dimethylphosphoryloxy)methyl substituent in A, rather than from the difference in the nucleophilicity of the nitrogen atoms.

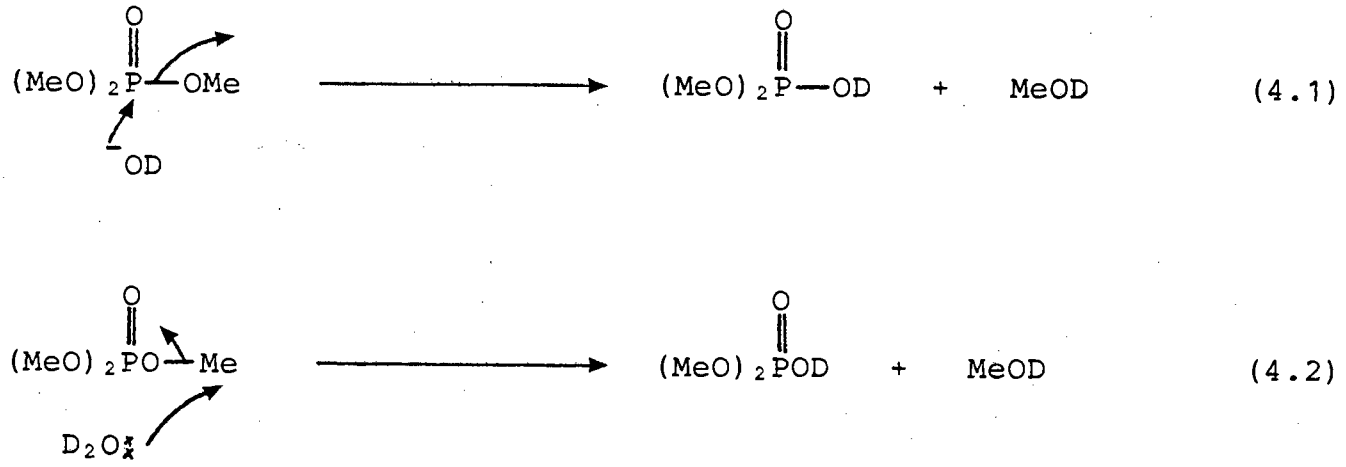
The lability of A in aqueous media is, however, markedly different and we have found that refluxing A in water, resulted in a considerable change in the ^{1}H NMR spectrum. Figure 4.1 shows that after refluxing A in D_2O (1.7M solution) for 2 h, there is no starting material remaining. We believe that this spectrum is essentially that of the zwitterion 4.1 (spectral yield: 88%). This assignment is based on the following: the N-methyl absorption at δ4.42 is observed; the doublet for the methylene group is shifted downfield to δ5.43 relative to its chemical shift position in A (Δδ0.18); the absorption for the pyridyl protons is shifted downfield from δ7.47 - 8.53 in the parent compound to δ7.97 - 9.02 in the product (the downfield shift of the pyridyl and methylene protons is due to the positive charge on the pyridyl nitrogen which causes the protons to become more deshielded); the doublet for the O-methyl absorption has shifted highfield to δ3.64 (from δ3.83 in the starting compound) which is expected because of the negative

charge development in the phosphate function; and the intensity of the O-methyl signal relative to the remaining signals (pyridyl hydrogens, methylene group) has been reduced to half of its initial value.

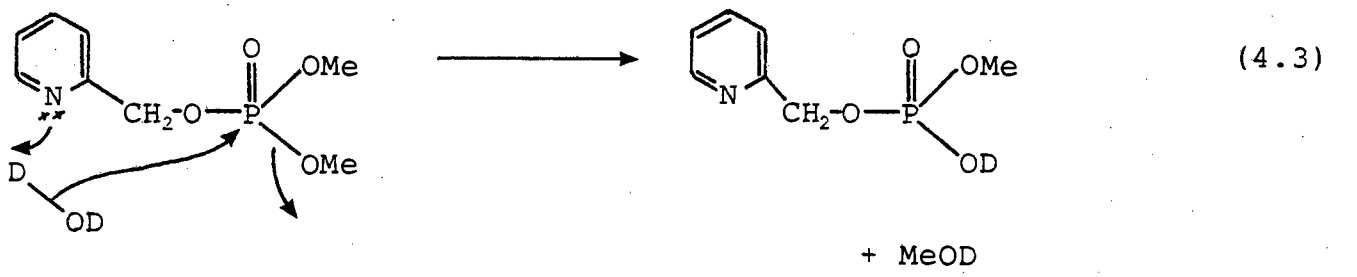
Figure 4.1



In addition, a side reaction involving hydrolysis of the substrate occurs and is responsible for the singlet at δ3.40 which is assigned to CH_3OD. This is the only other product observed, formed by the hydrolysis of A and/or 4.1 and it accounts for *ca.* 12% of the total reaction pathway. In an independent experiment involving refluxing TMP in D_2O for 2 h, a comparable quantity of methanol was obtained. We are not in a position to unambiguously state whether CH_3OD formation occurs as a result of either deuteroxide ion attack at the phosphorus atom (eq. 4.1) or neutral water (D_2O) attack at the methyl carbon atom (eq. 4.2).



Although both eq.s are in keeping with the first reports in 1958[47] that "soft" nucleophiles attack the alkyl group of trialkyl phosphates while "hard" bases attack the "hard" phosphorus atom, we suspect that the second reaction (eq. 4.2) is more probable as the control reaction was carried out in neutral water. It is unlikely that general base catalysis (eq. 4.3) is operating, as not only is the methoxy substituent a poorer leaving group than the 2-pyridylmethyloxy moiety, but the amount of MeOD formed in the reaction of A in water is comparable to that in the control reaction.



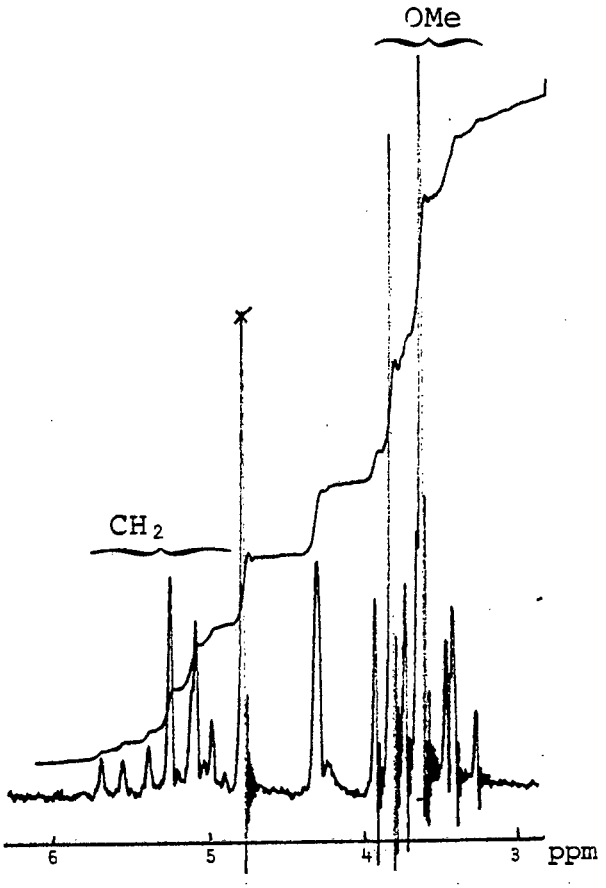
If the isomerisation of A was a bimolecular process (pathway α, scheme 4.1), two additional phosphates, the N-methylated substrate

($\underline{AI}^+$) and the O-demethylated substrate ($\underline{AI}^-$) should appear in the reaction mixture as intermediates. As the particular reaction conditions mentioned above resulted in complete reaction (fig. 4.1 shows no starting compound), we decided to follow the reaction using a less concentrated solution, with a view to observing the intermediates ($\underline{AI}^+$ and $\underline{AI}^-$). The reaction was repeated using a 0.9 M solution of substrate and after heating for 2 h under reflux a more complex mixture of products was formed. In addition to the signals corresponding to unreacted A (*ca.* 12%), 4.1 (*ca.* 63%) and methanol (*ca.* 15%),* the ^{1}H NMR spectrum of the solution revealed signals which could reasonably be assigned to the monocation ($\underline{AI}^+$) and monoanion ($\underline{AI}^-$). The spectrum of the mixture showed three distinct doublets for the methyl phosphate group (the fourth doublet is partially masked) - see fig. 4.2. Fortunately, complete assignment of these signals is possible: the zwitterion 4.1 was independently synthesized; when A was treated with dimethyl sulphate (N-methylation) and with sodium iodide (O-demethylation), the chemical shifts for the O-methyl group absorptions for $\underline{AI}^+$ and $\underline{AI}^-$, respectively, were obtained. (see ch. 4.1.3 for these preparations). The O-methyl groups of $\underline{AI}^+$ appear as the most lowfield O-methyl doublet at δ3.97 (J = 11 Hz) and the O-methyl group of $\underline{AI}^-$ appears as the most highfield (although partially masked by the O-methyl absorption of the zwitterion) O-methyl doublet at δ3.64 (J = 11 Hz). The shift lowfield ($\Delta\delta$0.14) and highfield

*It is evident from the singlet at δ3.40 which we assign as MeOD (on the basis of spiking the reaction mixture with authentic methanol) that hydrolysis is once again complicating the reaction.

($\Delta\delta$0.19) for $\underline{AI}^+$ and $\underline{AI}^-$ respectively from the absorption of the neutral substrate molecule are expected because of the development of the fully charged monocationic and monoanionic species.

Figure 4.2



Also obvious from the ^{1}H NMR spectrum of the product mixture are 4 distinct doublets for the -CH_2-O-P grouping. Full assignment of these doublets is possible because of the independent synthesis of the intermediates and the zwitterionic product.

These experiments reveal a pronounced solvent effect on the rate of alkylation of the nitrogen atom by the alkyl phosphate function, with the reaction proceeding notably faster in water than in any other solvent, even of high polarity. Besides this, the last two mentioned experiments also provide evidence for concentration affecting the rate of methyl transfer. Although we are confident

that our assignments of the intermediates $\underline{AI}^+$ and $\underline{AI}^-$ in the previous experiment are correct, it still remains to be seen whether the reaction is proceeding entirely by a bimolecular (intermolecular) mechanism with the exclusion of the intramolecular reaction pathway, or whether both pathways are operating. As concentration effects will be experienced for both bimolecular and unimolecular reactions, further experiments of a more quantitative nature are required before unambiguous elucidation of the reaction pathway can be made. This is investigated independently in part 4 of this chapter.

4.1.3 THE SYNTHESIS OF COMPOUNDS INVOLVED IN SCHEME 4.1, - 4.1, $\underline{AI}^+$ AND $\underline{AI}^-$

The validity of our ^{1}H NMR assignments for the zwitterionic product 4.1, the N-methylated substrate $\underline{AI}^+$ and the O-demethylated substrate $\underline{AI}^-$ in the isomerisation of dimethyl-(2-pyridylmethyl) phosphate are corroborated by the isolation of 4.1 from the reaction mixture and by the independent synthesis and ^{1}H NMR characterization of the intermediates $\underline{AI}^+$ and $\underline{AI}^-$.

Methyl-[2-(N-methylpyridinium)methyl] phosphate, 4.1

As the isomerisation reaction proceeds smoothly with little interference from competing side reactions, we decided to isolate the zwitterion 4.1 directly from the final product mixture.

The substrate A was heated in D_2O in a water bath at 60°C for 6 days after which time the ^{1}H NMR spectrum showed neither substrate nor intermediates present. The hydrolysis products (methanol and

demethylated substrate - $\underline{AI}^-$) accounted for *ca.* 15% (calculated spectroscopically) of the reaction mixture. After removing the D_2O and methanol under reduced pressure, the crude product was purified by reverse-phase column chromatography using a methanol: water mixture (4:1) as eluant. The fraction was recrystallized from isopropanol and yielded compound 4.1 as small white crystals of analytical purity.

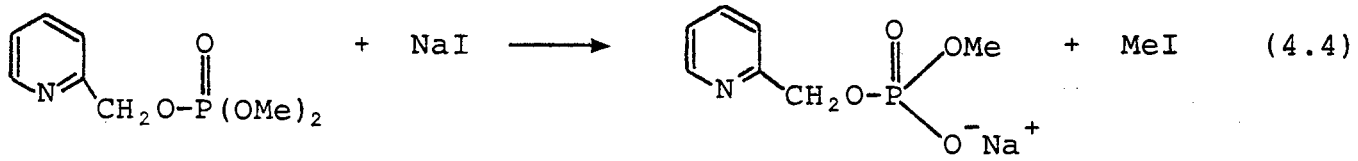
Dimethyl-[2-(N-methylpyridinium)methyl] phosphate methylsulphate, $\underline{AI}^+$

The procedure followed is similar to that used in the N-methylation of α-hydroxyphenazine[48] in the synthesis of pyocyanine. The methylation was effected by adding an excess of dimethyl sulphate (DMS) to substrate A, heating the reaction mixture for 1 h at 100°C and leaving it to stir overnight at room temperature. Most of the excess of DMS was removed by washing the mixture several times with diethylether and this afforded a viscous orange/brown syrup. NMR spectroscopy was used in the characterization of $\underline{AI}^+$ and complete methylation of A was indicated by total absence of A in the ^1H NMR spectrum along with the fact that the ratio of the intergration for the N-methyl singlet at δ4.43 to the intergration of the peak areas for the pyridyl, methylene, P-O-methyl and S-O-methyl protons was in the expected ratio. The introduction of a positive charge at nitrogen is manifested in the downfield shift of the pyridyl, methylene and O-methyl protons in the quarternized product (to lowfield) in comparison to the substrate. For example, the doublet corresponding to the methylene protons has shifted from δ5.25 to δ5.68, the O-methyl doublet has shifted from δ3.83 to δ3.97 and the range for the pyridyl protons has shifted from δ7.47 - 8.53 to δ8.03 - 9.17. $\underline{AI}^+$ is therefore adequately characterized by

the NMR spectrum. Analytically pure $\underline{AI}^+$ could not be obtained despite further efforts to remove traces of DMS by additional washings with ether and benzene.

Sodium Methyl-(2-pyridylmethyl) phosphate, $\underline{AI}^-$

The dealkylation and debenzylation of triesters of phosphoric acid by sodium or barium iodide is well known and has been reported in the literature.[49] The reaction results in the cleavage of a single primary alkyl-oxygen (or benzyl oxygen) bond and does not proceed beyond the formation of the diester. In fact this method provides a general and simple approach to the synthesis of phosphoric acid diesters and has the advantage that the triester need not be pure. This procedure has also found application in the field of blocking and deblocking of phosphate groups which has proved important in nucleotide synthesis.[50] The preparation of the sodium salt of methyl-(2-pyridylmethyl) phosphate was therefore carried out by refluxing the triester precursor - dimethyl-(2-pyridylmethyl) phosphate, with sodium iodide in acetone. Equation (4.4) represents the expected reaction.



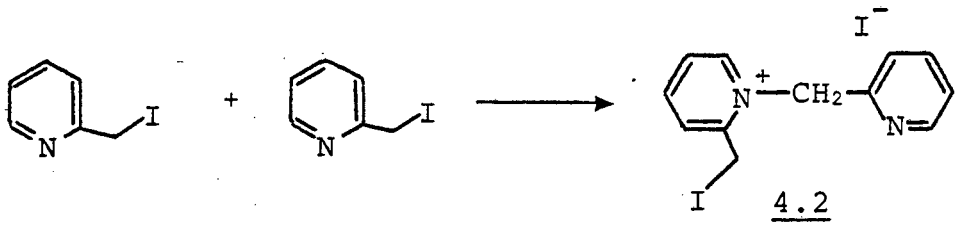
(4.4)

Through the use of an air condensor and a solvent having a higher boiling point than methyl iodide, the methyl iodide generated during the demethylation should theoretically be boiled off, and therefore the possible methylation of the pyridine nitrogen should be avoided.

Dimethyl-(2-pyridylmethyl) phosphate was heated under reflux for 4 h with a stoichiometric equivalent of sodium iodide which was dissolved in acetone. Unexpectedly the sodium salt of the diester did not precipitate out of the orange-coloured solution. Removal of the solvent under reduced pressure yielded a red oil, the ^1H NMR spectrum (D_2O) of which, was found to contain the desired phosphate diester (0.62 mole fraction) together with unreacted substrate (0.19 mole fraction). Evidence for the demethylation was found firstly in the upfield shift of both the methyl and methylene doublet in relation to the substrate ($\Delta\delta$0.19 and $\Delta\delta$0.20 ppm, respectively), and secondly in the integration of the phosphate ester methyl doublet for only three protons.

In addition to the required product and some starting material, a doublet at δ3.59 having the same coupling constant as the P-O-CH_3 doublet of the diester was tentatively assigned to dimethyl phosphate formed by the anionic cleavage of the O-$CH_2C_6H_5N$ bond. Addition of authentic sodium salt of dimethyl phosphate to the ^1H NMR mixture confirmed this assignment. As no singlet corresponding to the methylene protons of 2-pyridylmethanol was observed, we propose that dimethyl phosphate formation followed from the nucleophilic attack of iodide anion at the methylene carbon atom of the substrate, and this also resulted in the formation of 2-iodomethyl pyridine. Although confirmation of 2-iodomethyl pyridine in the ^1H NMR spectrum was more difficult, we did observe singlets at δ4.60 and δ4.32. We believe these singlets could correspond to the methylene protons of this compound and/or to 'self alkylated' dimeric or polymeric material. 2-Iodomethyl pyridine is a non-volatile alkylating agent which would remain in the reaction

solution and become alkylated by another molecule as shown in eq. 4.5. This reaction is envisaged as the beginning of a polymerization reaction.



(4.5)

4.2

We expect the methylene protons in both the substrate and the product of this reaction to be sufficiently acidic to undergo H/D exchange and we postulate this to be the reason why the intergration for both singlets was *ca.* 50% of that required (based on the intergration for dimethyl phosphate).

2-Iodomethyl pyridine is not easily accessible and a literature search disclosed that its preparation had not been reported. Following a report by Daub and Castle[51] for the synthesis of some substituted benzyl iodides, we attempted to synthesize 2-iodomethyl pyridine by simply treating the corresponding pyridylcarbinol with an excess of hydroiodic acid. Neutralization of the product - the salt of 2-iodomethylpyridinium iodide would than afford the desired product. However, we experienced some difficulty with this synthesis not only because neutralization by base to the neutral product is such a sensitive step, but also because of the alkylation shown in eq. 4.5.

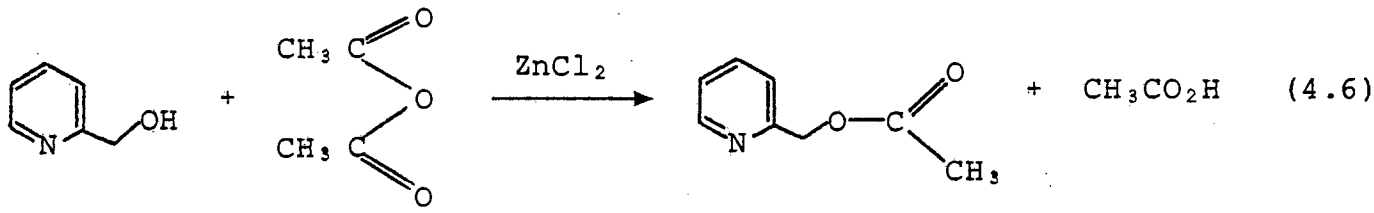
Instead of continuing to try and characterize 2-iodomethyl pyridine, we decided to rather separate the two sodium salts in order to obtain the pure sodium salt of methyl-(2-pyridylmethyl) phosphate. This was attempted by dissolving the reaction mixture in a minimum

volume of acetonitrile and pouring the solution into a large volume of ether. A white precipitate immediately fell out of solution but attempts to isolate the salt by centrifugation were not possible due to the extremely deliquescent nature of the salt. Removal then of the solvents *in vacuo* revealed that indeed purification had almost entirely separated sodium dimethyl phosphate from the product salt. Since the product is very hygroscopic and liquifies upon contact with air, it was not characterized by elemental analysis. Characterization by ^{1}H NMR spectroscopy was adequate for our purposes (identification of the product in a reaction mixture).

In connection with our investigation regarding the behaviour of compound A, we decided to prepare the acetate analogue of the phosphate A, compound E.

4.1.4 THE SYNTHESIS OF (2-PYRIDYLMETHYL) ACETATE, (E)

One of the most popular and well-documented routes to the synthesis of acetates is *via* the use of acid chloride as the acetylating agent. However, this results in the formation of hydrochloric acid, which is unfavourable if there are basic centres present in the substrate. Indeed having already encountered synthetic difficulties during the preparation of dimethyl-(2-pyridylmethyl) phosphate because of the susceptibility of the pyridyl nitrogen to protonation (see ch. 3.2), we chose acetic anhydride as the acetylating agent. The reaction is shown in eq. 4.6.



(4.6)

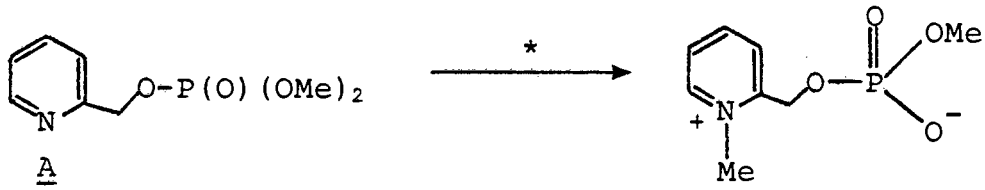
After heating acetic anhydride and zinc chloride together for 10 minutes, 2-pyridylmethanol was added to the cooled solution while stirring gently to control the vigorous reaction which ensued. The reaction vessel was then heated for 1 h on a hot plate. The solution was cooled and poured into iced water, stirring vigorously to assist in the hydrolysis of unreacted acetic anhydride. The product was extracted with ethyl acetate, dried with anhydrous magnesium sulphate and the solvent removed *in vacuo* to leave an oil. ^{1}H NMR spectroscopy showed this to be a mixture of the expected

acetate and unreacted 2-pyridylmethanol. The pure product was obtained by column chromatography using chloroform : ethanol (4:1) as eluant. ^{1}H NMR spectroscopy, elemental analysis and mass spectrometry (see ch. 7) confirmed the purity of the acetate.

4.1.5 O → N METHYL TRANSFER IN 2-PYRIDYLMETHYL DERIVATIVES

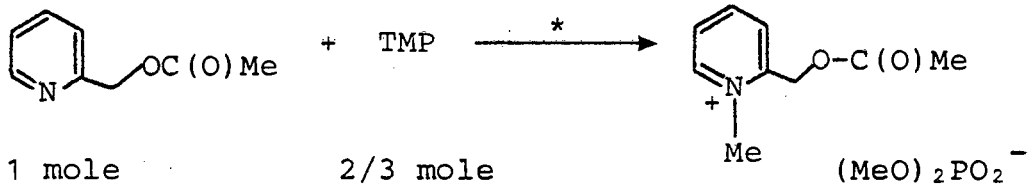
Attention was next focussed on the comparison of O → N methyl group transfer in the three systems shown below.

SYSTEM I



A (4.7)

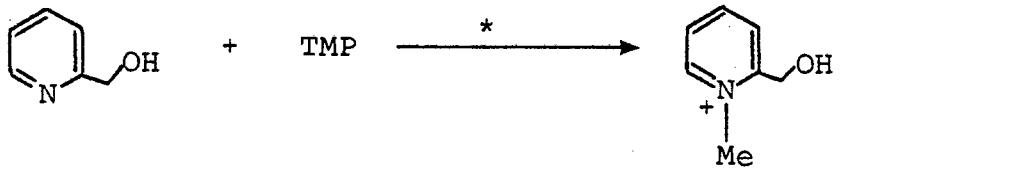
SYSTEM II



1 mole 2/3 mole (4.8)

E

SYSTEM III



1 mole 2/3 mole (4.9)

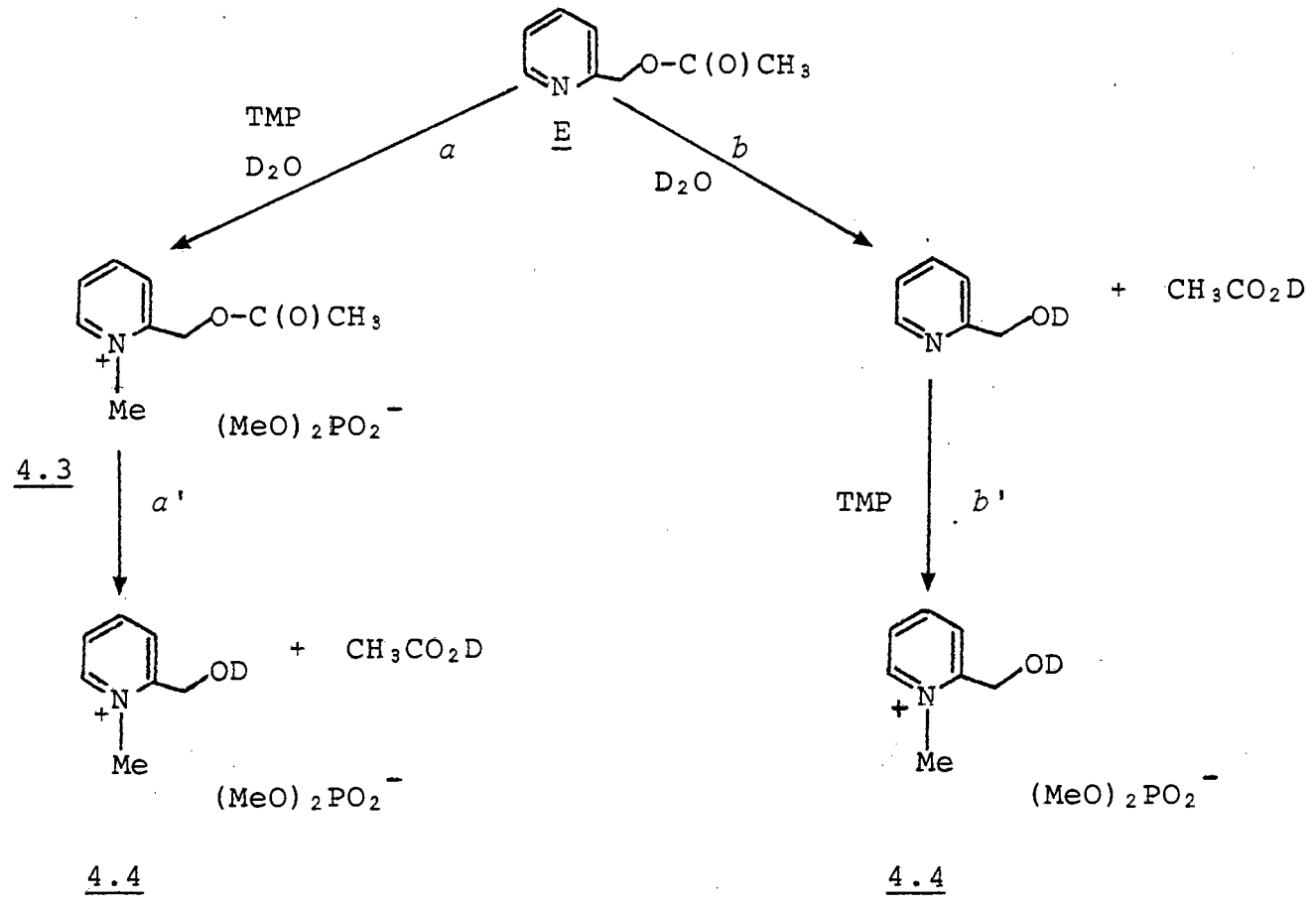
S

*Reflux 2 h in D_2O

Equation 4.7 has already been discussed in some detail and will now be considered from a comparative point of view in light of systems II and III. For the reactions represented by eq.s 4.8 and 4.9, statistical corrections for the number of methyl groups available in the methylating reagent (the phosphate ester) for the transfer reaction were made by using a 2/3 stoichiometric amount of TMP. For each experiment the substrates were weighed into a sample tube and a known volume of D_2O added. After mixing the contents of the flask, the solution was transferred to an NMR tube. The ^1H NMR spectrum was recorded to ensure that the stoichiometry for the reaction systems II and III was correct and then the tubes were sealed. After keeping the tubes in a boiling water bath for 2 h, they were placed in an iced water bath to arrest the reaction and their ^1H NMR spectrum recorded.

The results obtained for system I have already been discussed. Considering system II, there are 2 possible reaction pathways initially available for E under the given conditions and these are represented by pathway (*a*) and (*b*) in scheme 4.2.

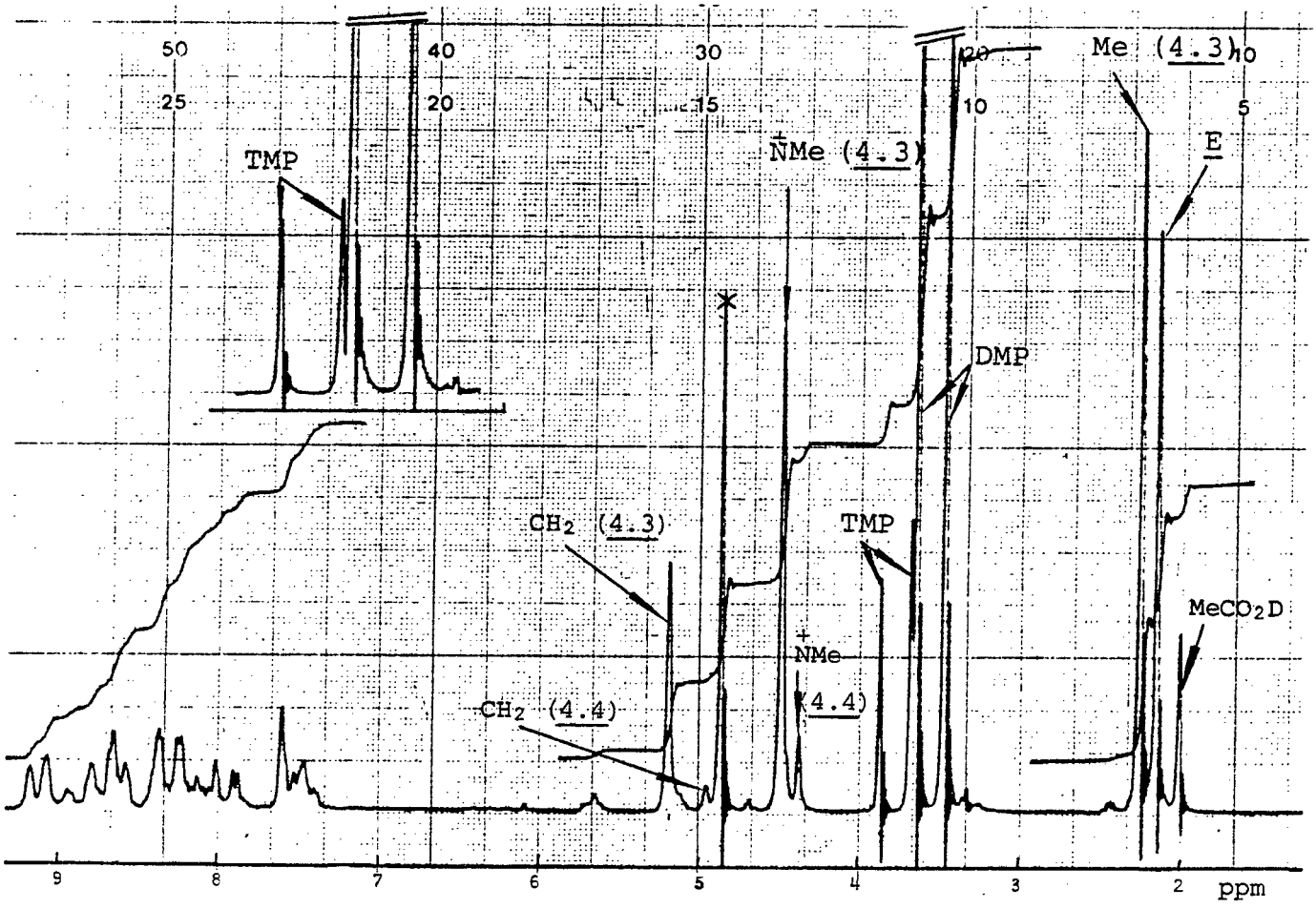
Scheme 4.2



The ^{1}H NMR spectrum of the reaction products in system II is shown in fig. 4.3. Figure 4.3 shows that 61% of substrate E has undergone conversion to products. This percentage value is based on the intergration of the peak area for the acetyl methyl group in E (s, δ2.18), relative to the total intergration for all acetyl methyl signals present. The N-methylated product 4.3, formed in the methyl transfer reaction (*a*) was identified by the acetyl methyl (s, δ2.30), the N-methyl (s, δ4.66), and the methylene (s, δ6.03) signals, and the yield of this product was 49%. The remaining products present in the reaction mixture are acetic acid (s, δ2.05) formed in 12% yield, together with the equivalent quantity of 2-(N-methylpyridinium) methanol, 4.4 (identified by its N-methyl and

methylene signals; δ4.55 and δ5.12 respectively). No free 2-pyridylmethanol could be detected in the reaction product, as indicated by the absence of the absorption characteristic for the methylene group of this compound (δ4.77). This is not surprising, since any 2-pyridylmethanol formed by the hydrolysis of E (pathway *b*) would undergo fast methylation by TMP to yield compound 4.4 (see later). It is therefore not possible in this experiment, to determine whether the second N-methyl product, 4.4 is formed from 4.3 *via* the hydrolysis reaction (pathway *a'*) or *via* the independent route (*b*), followed by (*b'*). The extent of the methyl group transfer from TMP to E can therefore be determined as being in the range of 49 to 61%. Further discussion on fig. 4.3 regarding hydrogen/deuterium (H/D) exchange is dealt with in ch. 4.1.6.

Figure 4.3



The third system studied provides information regarding pathway *b'* in scheme 4.2. Treatment of 2-pyridylmethanol with TMP in D_2O under the conditions previously described resulted in 92% O→N methyl transfer. The sharp singlet at δ4.55 in the ^1H NMR spectrum of the reaction products for this system, is assigned to the N-methyl absorption of the product and this chemical shift corresponds to that of the second N-methyl absorption observed in the ^1H NMR spectrum from system II.

In order to directly compare our results, the assumption that all reactions of methyl transfer are bimolecular must be made. For example, we can derive eq. 4.14 which gives the ratio of the second-order rate constant ($k_{2\,(PO)}$) for the reaction of the phosphoryl (P = O) containing compound A, to the second-order rate constant ($k_2'_{(CO + TMP)}$) for the reaction of the carbonyl (C = O) compound E, with TMP.

The rate of reaction in systems I and II are firstly given by eq. 4.10 and 4.11, respectively.

$$\text{Rate} = k_{2\,(PO)}\,[\underline{A}]^2 \qquad (4.10)$$

$$\text{Rate} = k_2'_{(CO + TMP)}\,[\underline{E}][TMP] \qquad (4.11)$$

As the rates of reaction are measured in terms of the % O→N methyl transfer determined after the same period of time and under the same conditions for all systems, eq.s 4.10 and 4.11 can be rewritten as 4.12 and 4.13, respectively.

$$\%\ O\rightarrow N \text{ methyl transfer (I)} = k_{2\,(PO)}\,[\underline{A}]^2 \qquad (4.12)$$

$$\% \ O \rightarrow N \text{ methyl transfer (II)} = k_{2\,(CO + TMP)} [\underline{E}][TMP] \qquad (4.13)$$

which expressed as a ratio gives

$$\frac{\% \ O \rightarrow N \text{ methyl transfer (PO)}}{\% \ O \rightarrow N \text{ methyl transfer (CO + TMP)}} = \frac{k_{2\,(PO)} [\underline{A}]^2}{k_2{}'_{(CO + TMP)} [\underline{E}][TMP]}$$

or

$$\frac{k_{2\,(PO)}}{k_2{}'_{(CO + TMP)}} = \frac{\% \ O \rightarrow N \text{ methyl transfer (PO)} \times [E][TMP]}{\% \ O \rightarrow N \text{ methyl transfer (CO + TMP)} [\underline{A}]^2} \qquad (4.14)$$

Similarly a comparison of the results for systems I and III and II and III can be obtained by treating the results given below in table 4.1 in an analogous manner. The table includes the additional results from the reaction of TMP and pyridine.

Table 4.1 Results of O→N methyl transfer in dimethyl-(2-pyridylmethyl) phosphate, and for 2-pyridylmethyl acetate, 2-pyridylmethanol and pyridine with trimethyl phosphate

Substrate[a]	Time at 100°C (minutes)	% $\overset{+}{N}$-CH_3	k_{rel}[b]
<u>A</u>	20	62	0.47[c]
<u>E</u> + $(MeO)_3PO$	120	52	0.43 - 0.49[d]
<u>S</u> + $(MeO)_3PO$	120	92	0.75 - 0.87[d]
	30	81	
	20	66	
C_6H_5N + $(MeO)_3PO$	30	93	1
	20	88	

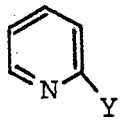
[a] Initial concentration of <u>A</u>, <u>E</u>, <u>S</u> and C_6H_5N = 3.2 <u>M</u>. The initial concentration of TMP was corrected for the number of methyl groups present in the methylating agent.

[b]Because of step-wise comparisons involved, k_{rel} values should be taken as semi-quantitative.

[c]This value is obtained not from a direct ratio of percentages of conversions, but includes the differences in concentrations of species involved (see eq. 4.14).

[d]The range of k_{rel} values obtained results from four different ratios of conversions obtained for different reaction periods.

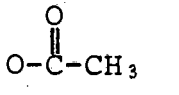
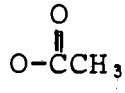
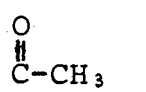
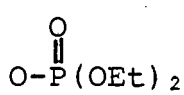
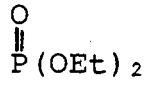
Pyridine can be considered as the most simple system related to A, S and E and can be used as a reference model compound in which a study of the effect of substituents in the α-position to the nucleophilic pyridyl nitrogen, on the methyl transfer reaction, can be made. It is conceivable then that the reaction of TMP with pyridine, 2-pyridylmethanol and 2-pyridylmethyl acetate decrease in this order. To check this proposal we carried out the additional experiment with pyridine and the result was in accord with our expectations. The results from table 4.1 enable us to obtain the following order of decreasing reactivity in the O → N methyl transfer reaction for the following 2-substituted pyridine series:

Y in  = H > CH_2OH > $CH_2OP(O)(OMe)_2$ ≙ $CH_2OC(O)Me$ (4.15)

We were interested in the position of dimethyl-(2-pyridylmethyl) phosphate in the above series, aware that the bifunctional nature of the compound introduces structural differences which will not only affect the nucleophile, but will also alter the methylating

ability of the electrophile. However, irrespective of the nature of the methylating agent, on steric grounds alone, it is expected that the dimethylphosphoryloxy methyl substituent in compound A would result in the pyridyl nitrogen being less susceptible to methylation than 2-pyridylmethyl acetate and certainly less than 2-pyridylmethanol. A comparison of the Taft substituent constant values σ^* or the electron withdrawing effects as described by the inductive parameter σ_I for the groups given in table 4.2 shows that the electronic effects of the substituents in A and E are not widely different. The similarity in the values suggests that dimethyl-(2-pyridylmethyl) phosphate and 2-pyridylmethyl acetate should have comparable reactivities in regard to O → N methyl transfer.

Table 4.2 σ^* and σ_I values of selected groups

	σ^*		σ_I
	2.56[52]		+ 0.46[45]
	1.81[52]		+ 0.58[45]
	2.18[53]		

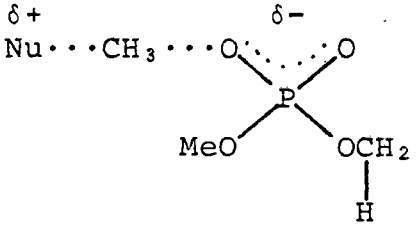
Equation 4.15 enables a comparison to be made between the detailed structure of the substrate molecules with their reactivity. Firstly, despite the fact that a strong intramolecular hydrogen bond has been found[54] to be present in 2-hydroxymethyl pyridine, we believe that in aqueous medium, this effect diminishes through intermolecular hydrogen bonding and the difference in the reactivity of

E and S towards TMP in D_2O can be explained by the electron withdrawing effect of the acetyl substituent which then renders the pyridyl nitrogen atom less nucleophilic. In addition, the effect of *ortho*-alkyl substituents on quarternization of pyridines was recognised long ago to be steric in character.[55] There is greater steric bulk at the 2-position in E compared to S and this crowding offers further resistance towards the alkylation reaction. The lower reactivity of E compared to the substrate alcohol is in accord with the Taft substituent constant σ^* for the $-OCOCH_3$ group ($\sigma^* = 2.56$).

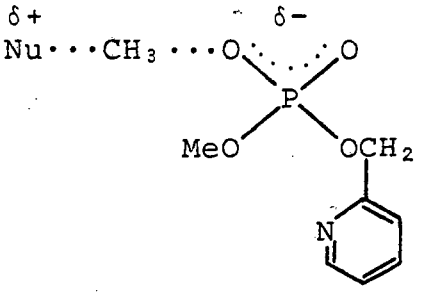
However, the most striking fact about the order of reactivity given in eq. 4.15 is that it does not follow expectations of reactivity based purely on electronic and/or steric demands of the nucleophile. We can explain the unexpected position of the dimethylphosphoryloxy methyl substituent in eq. 4.15 by the difference in the electrophilic reagent. The electron withdrawing effect of the $-CH_2OP(O)(OMe)_2$ substituent which makes the pyridyl nitrogen atom less nucleophilic, is more than compensated for by the electron withdrawing effect of the pyridyl substituent making the methyl groups in A more electrophilic than those in TMP. It is this more effective methylating ability of A compared to TMP which is responsible for the position of the phosphorus derivative in the above series.

An important fact from the aforementioned studies is that the reactions proceed most effectively in water as the reaction medium. When the reactions in systems I, II and III were repeated using acetonitrile as the solvent, less than 5% O → N methyl transfer

occurred. This observation substantiates our proposed transition state model discussed shortly in which we believe it is the strong hydrogen bonding between water and the departing diester-monoanion leaving group that is responsible for the pronounced solvent effect. Quite clearly the above results reveal that the leaving group must play an important role in the reaction. This interpretation is best explained by considering the transition state model for the reaction system. When TMP is the methylating agent, the transition state can be illustrated by 4.5. When dimethyl-(2-pyridylmethyl) phosphate is the methylating agent, the leaving group can be involved in the transition state represented by 4.6. In both 4.5 and 4.6, the negative charge can be delocalized over 2 oxygen atoms leading to stabilization of the transition state, but in addition to this, the electron withdrawing effect of the pyridyl group at the methylene carbon (4.6) compared to the hydrogen atom (4.5) is responsible for further stabilization in 4.6.



4.5



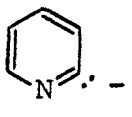
4.6

The results so far reported are of an exploratory nature and yet despite this, the facts reveal certain conclusions which we feel are worthy of being analyzed in greater detail. In ch. 8, an in-depth study of the effect of solvent on the reaction between TMP and pyridine and TMP and 4-(dimethylamino)-pyridine (4DMAP) at different temperatures enables a comparison of the activation

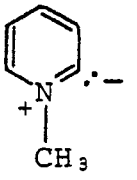
parameters obtained to be made. A knowledge of these thermodynamic terms may provide insight into the nature of the transition state (i.e. an early or late transition state) as well as possibly confirming our interpretation regarding the effect of hydrogen bonding.

4.1.6 HYDROGEN/DEUTERIUM EXCHANGE

An interesting observation from fig. 4.3 is the partial 'loss' of the methylene protons of the product. Both the positive charge on the pyridyl nitrogen as a result of methylation and the acetyl group cause the methylene protons to become more acidic and we believe these protons undergo exchange with deuterium atoms when D_2O is used as the solvent. In support of this statement, two groups of workers[56] have found that if the lone pair of electrons on the nitrogen atom of pyridine is bonded to a methyl group, then the rate of H/D exchange at the 2-position is much greater than at any other position. (Compare the respective carbanions 4.7 and 4.8.)



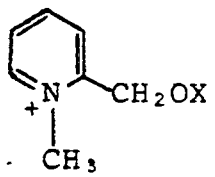
4.7



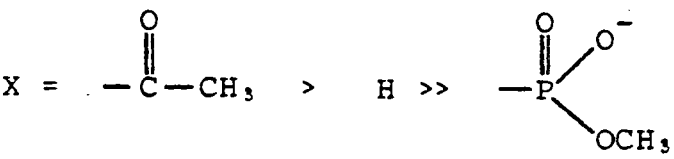
4.8

A closer examination of the ^1H NMR spectral features of the reaction product for system III reveal that only 75% of the methylene protons of the product are present and we believe that deuterium exchange is again responsible for this. This exchange was not observed

in the ^1H NMR spectrum of the reaction product for system I, compound 4.1, because although methylation of the pyridyl nitrogen atom causes the α-hydrogen to become more acidic, we believe the negative charge on this zwitterion acts to oppose the electron withdrawing effect The observed order of hydrogen-deuterium exchange in derivatives of type 4.9 is given in the series.

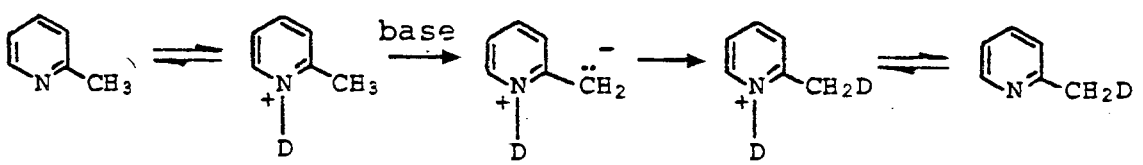


4.9



(4.16)

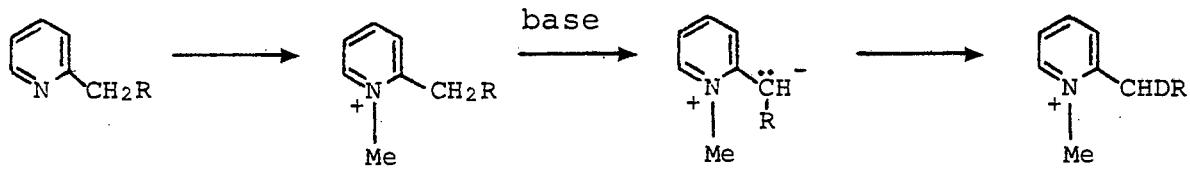
Although H/D exchange in the C-alkyl side chains of quarternized and unquarternized nitrogen containing heterocycles has been investigated thoroughly,[57] no literature data directly applicable to the aforementioned systems has been reported. Despite this, we believe that what evidence is present, supports our proposals of H/D exchange at the α-carbon atom of 2-substituted pyridines. Zoltewicz[57] claims that the mechanism of H/D exchange in the methyl groups of pyridines in dilute aqueous acid can be represented by the following equation.



(4.17)

This H/D exchange mechanism was established from results of serial dilution experiments and illustrates that the conjugate acid of the substrate, the N-deuteriopyridinium ion, is deprotonated by

the pyridine acting as a general base catalyst to give a dipolar intermediate, which in a subsequent fast step incorporates deuterium. Modification of this equation enables us to propose that H/D exchange occurs in N-methylated dimethyl-(2-pyridylmethyl) phosphate as shown in eq. 4.18.



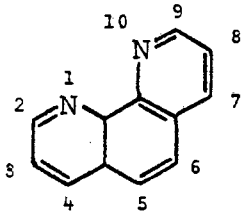
(4.18)

R = $OP(O)(OMe)_2$

In our view the above analogy is perfectly acceptable and the only limitation in comparing eq. 4.17 and 4.18 is the irreversible positive charge formation - methylation, of the pyridyl nitrogen in eq. 4.18. It is conceivable that H/D exchange can proceed one step further to give the dideuterated N-methylated pyridinium product, although complete 'loss' of the methylene proton absorptions from the ^1H NMR spectra was not observed under the given conditions. It would be very difficult, if not impossible to give a value to account for the percentage of mono- and di- H/D exchanged products as the ^1H NMR signal position of the N-methyl and methylene groups containing one or two deuterium atoms would appear as shoulders on the original singlet and doublet respectively as the exchange proceeded.

In favour of our argument that N-methylation increases the possibility for H/D exchange, is the need for protonation at N-3 of pyrimidines before deuterium exchange of the C-methyl protons

(C-2, C-4 and C-6) is possible.[58] In addition, it is clear from results of hydrogen exchange in 1,10-diazaphenanthrene (structure 4.10), where exchange occurs readily at C-2, C-3 and C-4 but not at C-5 and C-6, that exchange in neutral D_2O requires deuteration at nitrogen.[59]



4.10

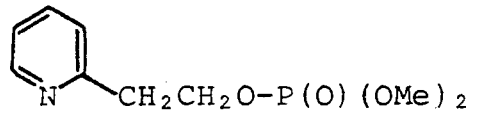
Finally experimental results in support of the above proposal were obtained by heating solutions of 2-pyridylmethanol (3.2 M) and β-(2-pyridyl)-ethanol (3.2 M) in D_2O in sealed NMR tubes, using the same internal standard as before, for 400 h at 60°C. No H/D exchange was observed in the methylene groups of either substrates and this confirms our belief that in the absence of acid or base catalysis, a positive charge on the pyridyl nitrogen is a necessary condition for the occurrence of H/D exchange.

We feel confident that the N-methyl protons in 4.9 do not exchange, as in the above study of pyrimidines,[58] the authors state that the peaks from the N-methyl protons did not exchange and these absorptions were in fact used as the reference with which to follow H/D exchange at other positions. Similarly in a study of deuterium exchange of C-methyl protons in lumazine derivatives,[60] and in an investigation into base-catalysed H/D exchange of N-substituted pyridinium ions,[61] the N-methyl groups were unreactive.

However, in order to confirm this lack of lability of the methyl hydrogens of the N-methylpyridinium system, we carried out the following experiment. A 1 M solution of N-methylpyridinium iodide in D_2O was heated for 68 h at 90°C in a sealed NMR tube, using the sodium salt of 3-(trimethylsilyl)-propanesulfonic acid (DSS) as the internal standard. Measurement of the peak area under the peaks showed no exchange. With base-catalysed H/D exchange in mind, we added 0.2 mole equivalents of pyridine to the solution and heated the mixture for a further 68 h at the same temperature. Any change in the peak area ratios was within the limits of experimental error and this enabled us to conclude that our results are in accord with the literature, in so far as the N-methyl protons did not exchange.

4.2 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-[β-(2-PYRIDYLETHYL)] PHOSPHATE, B.

4.2.1 INTRODUCTION



B

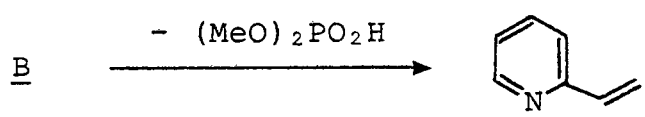
Our interest in compound B stems from the fact that there is an additional methylene group (compared to compound A) in the pyridyl ester substituent. The semi-quantitative study of O→N methyl transfer in dimethyl-(2-pyridylmethyl) phosphate has revealed evidence for the reaction occurring *via* the intermolecular mechanism (the results obtained at this stage do not allow us to state whether this occurs exclusively). However, if this is so, then we foresee the possibility of some intramolecular participation in the O→N methyl transfer reaction for substrate B because of the larger ring - an 8-membered ring which could form in the cyclic transition state (see ch. 3.1).

The results obtained from the kinetics of the base-catalysed hydrolysis of bis-(p-nitrophenyl)[β-(2-pyridylethyl)] phosphate give no evidence for intramolecular nucleophilic catalysis. We can therefore conclude that any N→P interaction in B is highly improbable, more so because of the 2 methoxy groups as ester substituents.

The additional methylene group will, of course, introduce more signals in the ^1H NMR spectrum. This complicates the system as the quartet for the methylene protons α to the phosphorus atom is centered at δ4.47 which is in the chemical shift range of the $\overset{+}{N}$-Me absorption. The initial masking of the N-methyl signal by the substrate methylene protons and the fact that neither the triplet nor the quartet for the methylene proton absorptions of the product are shifted significantly from the methylene absorptions of the substrate, makes a study of the kinetics of the methyl transfer reaction considerably more complicated than in the 2-pyridylmethyl ester. However, by comparing the intergration for the two methylene groups, which in the absence of an N-methyl absorption will be in a 1:1 ratio, a semiquantitative estimate can be made for the extent of methyl transfer.

4.2.2 RESULTS

As with compound A, attention was firstly focussed on establishing the solvent effect, if any, on the reactivity of the substrate B, by refluxing it in various solvents. Compound B remained unchanged after being refluxed for 18 h in $CD_3C(O)CD_3$, $CDCl_3$, and 4.5 h in CD_3CN. However, after a further 6.5 h in refluxing CD_3CN, about 50% elimination, as represented by eq. 4.19, occurred.

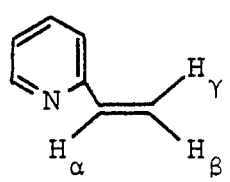


(4.19)

The reaction product was identified by ^{1}H NMR spectroscopy and the spectral pattern for the vinyl protons was well resolved* and in agreement with the literature values.[62] From our point of view, the elimination reaction is a secondary reaction and not of any importance to the O→N methyl transfer under study. There was no evidence for an $\overset{+}{N}$-Me signal. Similarly in a DMSO-d_6 solution at 30°C, no O→N methyl transfer was observed after 40 days. In fact a remarkable stability of this compound was observed - it was unchanged after being kept at room temperature for 40 days and after 14 months in a refrigerator at 10°C, only 30% elimination (eq. 4.19) had occurred.

Once again it is the reaction in water (D_2O) which proves the most interesting, as this is the only solvent which promotes O→N methyl group transfer. In fact refluxing B in D_2O for 2 h gave 100% O→N methyl transfer based on the absence of substrate from the ^{1}H NMR spectrum and on the singlet at δ4.52 which is assigned to the N-methyl absorption. The additional methylene group not only complicates the ^{1}H NMR spectrum but also provides the system with the potential for an elimination reaction. The vinyl protons characteristic of the elimination product are observed and the shift downfield of the β proton of the vinyl group from δ5.65 in neutral 2-vinylpyridine to δ6.27 in the present case clearly suggests that the pyridyl N atom carries a positive charge. Scheme 4.3

*



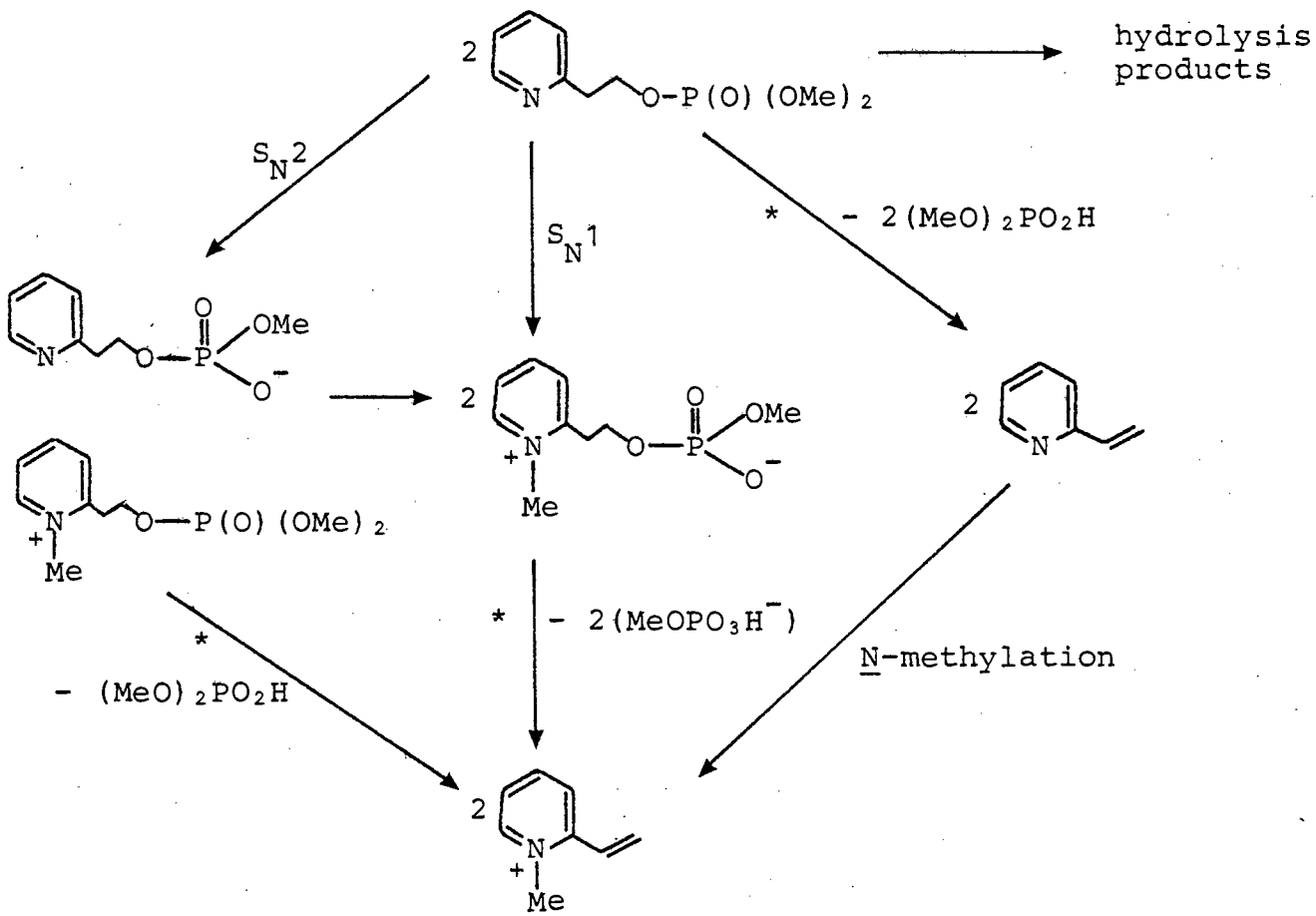
4.11

Observed values

H_α	δ7.05, d,d	$H_{(\alpha)}$-$H_{(\beta)}$	*ca.* 9 Hz
H_γ	δ6.37, d,d	$H_{(\beta)}$-$H_{(\gamma)}$	*ca.* 2 Hz
H_β	δ5.65, d,d	$H_{(\gamma)}$-$H_{(\alpha)}$	*ca.* 17 Hz

shows the possible reaction pathways for substrate B in an aqueous solution. Not included in this scheme are the hydrolysis products of the substrate. The production of methanol would be accompanied by the formation of methyl-[β-(2-pyridylethyl)] phosphate which in turn, could undergo elimination followed by N-methylation or N-methylation followed by elimination. The contribution of this pathway to the final reaction products is suspected as being of a similar magnitude as that observed for the 2-pyridylmethyl derivative (i.e. *ca*. 12%).

Scheme 4.3



*Elimination reaction

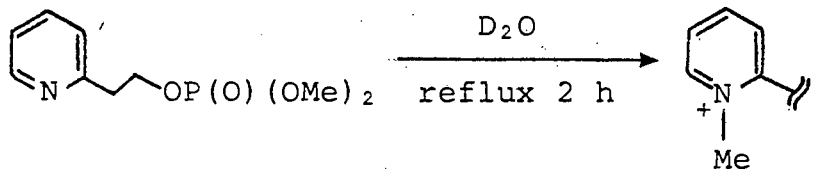
The complexity of the ^1H NMR spectral features of the reaction product does not enable us to reach any sound conclusions regarding the nature of the methyl transfer mechanism which is fraught with side reactions as a consequence of the additional methylene link. Intuitively from the results obtained for the 2-pyridylmethyl derivative, we suspect that the bimolecular reaction mechanism predominates.

4.2.3 O → N METHYL TRANSFER IN β-(2-PYRIDYLETHYL) DERIVATIVES

Since we had found that the pyridyl nitrogen in substrate B undergoes complete methylation (probably via the bimolecular mechanism) after refluxing for 2 h in D_2O, we decided to compare the reactivity of B with that of the two closely related substrates - the parent alcohol - β-(2-pyridyl)-ethanol, and its acetate - compound F. As these two substrates do not, of course, contain a methylating group, their reactivity was studied using TMP (systems V and VI, respectively) as a methylating agent and the results were then compared with the "self-methylation" of B (system IV).

Compound F was prepared according to the general experimental method already described for (2-pyridylmethyl) acetate in 4.1.4. However, one simple albeit necessary adjustment had to be made. Initially when the reaction was attempted only 20% product was formed. 80% of the reaction mixture consisted of 2-vinylpyridine and acetic acid. This clearly illustrates that elimination is an intrinsic property of a β-phenylethyl system. The synthesis was therefore carried out at room temperature, stirring for 18 h. These reaction conditions afforded only the pure acetylation product.

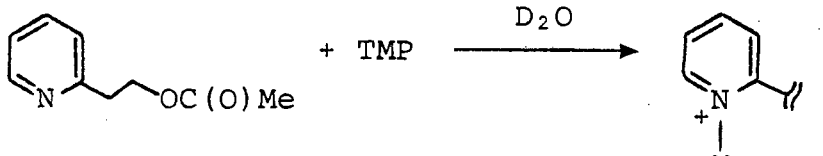
SYSTEM IV*



100%

(4.20)

SYSTEM V*



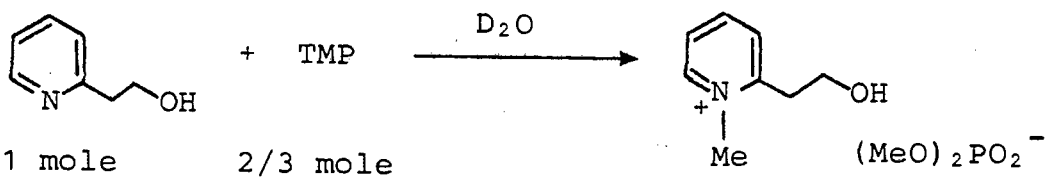
F 1 mole 2/3 mole

(4.21)

Va Reflux 2 h

Vb T = 60°C

SYSTEM VI



1 mole 2/3 mole

(4.22)

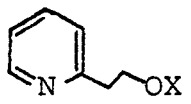
VIa Reflux 2 h

Vb T = 60°C

*Reactions involving the side chain of the substrate molecule will be discussed later.

As shown in eq.s 4.21 and 4.22, statistical corrections were made for the number of methyl groups present in the alkylating agent by using a 2/3 stoichiometric equivalent of TMP. These reactions were carried out in a manner analogous to those already described for systems II and III.

The amount of TMP consumed can be used as a basis on which to calculate the percentage O → N methyl transfer. (Under these conditions the extent of TMP hydrolysis is negligible.) However, for both compound F and the parent alcohol as for substrate B (see ch. 4.2.2), the methyl transfer is not the only possible reaction. For example, in compound F, elimination and/or hydrolysis can occur which therefore prevents a quantitative determination of the O → N methyl transfer. It is possible, however, to calculate the total* O → N methyl transfer as 75% and 85% for systems Va and VIa, respectively. For the general system 4.12, we therefore obtain the following decreasing order for O → N methyl transfer.



$X = P(O)(OMe)_2 > H > C(O)Me$

4.12

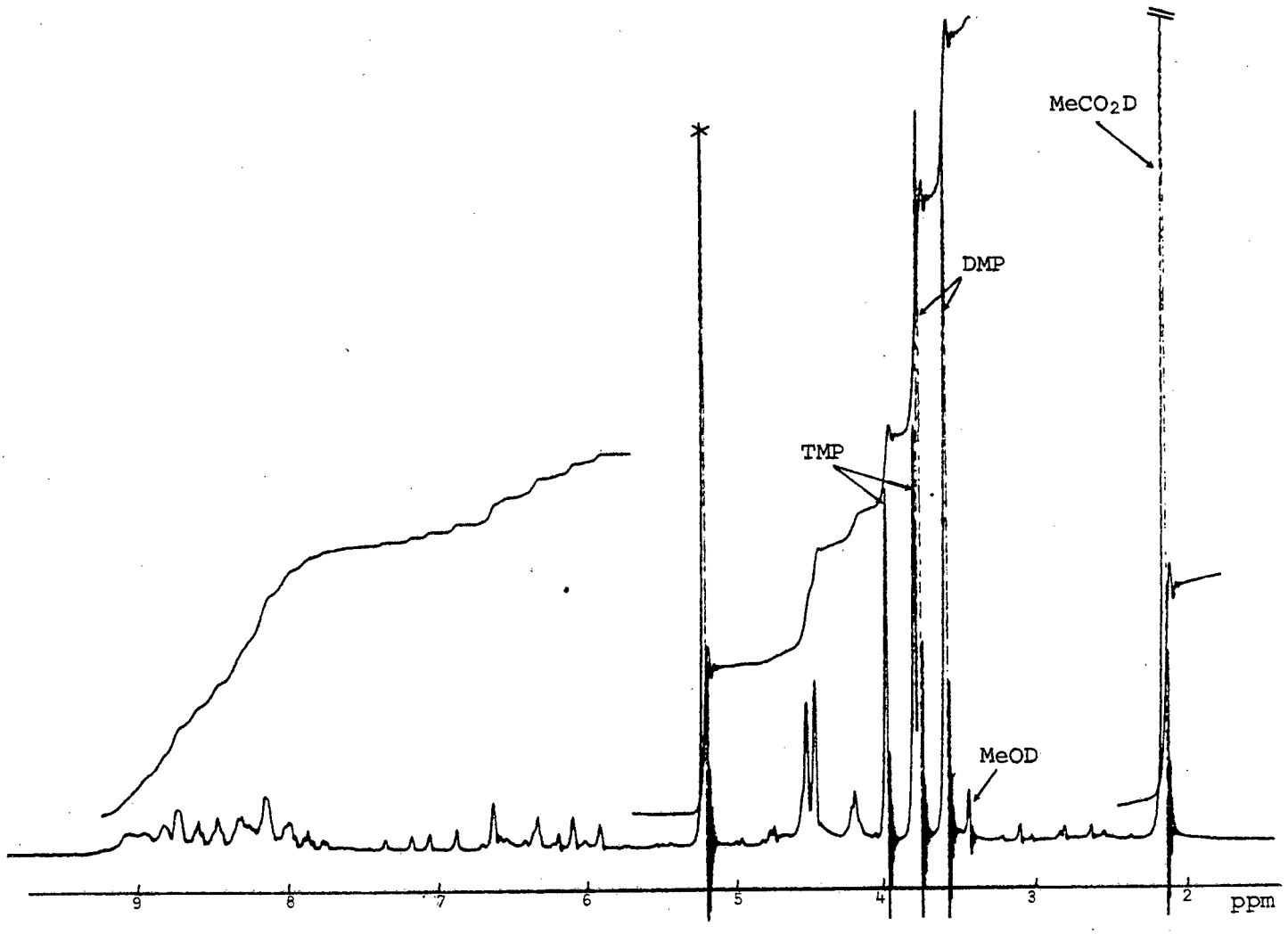
Although this order parallels the order observed in the 2-pyridylmethyl series (see eq. 4.12), the actual definition of methyl transfer given in the footnote below prevents a direct comparison

*Total O → N methyl transfer = methyl transfer to substrate and elimination and hydrolysis products.

of the amount of methyl transfer in the pyridylmethyl and pyridylethyl analogues to be made. The electron withdrawing effect of the acetate substituent renders the pyridyl nitrogen atom in compound F less nucleophilic than in β-(2-pyridyl)-ethanol and aside from electronic effects, steric bulk possibly also plays a part in the availability of the nitrogen electron pair. Using the same argument put forward in 4.1.4, we calculate that O → N methyl transfer is at least 30 x more advanced in the phosphoryl system (system IV) compared with the carbonyl system (system V).

The ^{1}H NMR spectrum of the reaction mixture from system Va is given in fig. 4.4.

Figure 4.4



Quite clearly it shows that the reaction is not as simple as it was initially expected and independent experiments were necessary before any conclusions pertaining to this spectrum could be made.

In order to test the stability of [β-(2-pyridylethyl)] acetate to hydrolysis, a 3.2 M solution of F was prepared in D_2O and heated in a sealed NMR tube at 60°C. Although [β-(2-pyridylethyl)] acetate was not soluble in D_2O at this concentration, the ^1H NMR spectrum was recorded periodically. After 5 days there was still no change in the spectrum and this result could be foreseen from the observation that the oil-like substrate still remained as the top layer in the tube.[63] However, after 6 days, the mixture was homogeneous and the ^1H NMR spectrum revealed that complete elimination had occurred. According to the spectral data, there was no substrate nor β-(2-pyridyl)-ethanol in the mixture. However, it could be calculated that *ca.* 75% H/D exchange had occurred at the carbon atom α to the pyridyl ring. There was no distinct doublet of doublets at δ7.05 which we assigned to the proton α to the pyridyl ring in 2-vinylpyridine (see 4.11). The intensity of the signal at δ7.1 was *ca.* 50% of that obtained for signals of β and γ hydrogen atoms (*ca.* δ5.9 and δ6.4). The *cis* and *trans* coupling constants for H_α were 10.8 and 18 Hz, respectively.[62] The literature values are quoted as 9 and 17 Hz, respectively. The chemical shift value of the α-proton was downfield of the literature value and we believe this was due to the presence of the positive charge at nitrogen in 2-vinylpyridinium acetate. In the absence of H/D exchange, H_β and H_γ both form a doublet of doublets, shifted upfield of H_α. However, H/D exchange at C_α causes distortion

of both H_β and H_γ and this was indeed obvious from the spectrum.

It must be remembered, however, that the H/D exchange in F can occur either from the substrate or from the hydrolysis product, or even possibly from the elimination product. Although the development of positive charge at nitrogen during the methylation reaction should facilitate the exchange, it is not a necessary prerequisite for the exchange. The carbanionic intermediate involved in the exchange reaction can be stabilized by the electron-accepting effect of the ring nitrogen. This reasoning is supported by work on ω-substituted picolines and methyl quinolines[64] where the possibility of positioning a portion of the anions negative charge on the electronegative nitrogen atom appeared to be the factor which determined the base-catalysed hydrogen-tritium exchange rate of these compounds. We believe that H/D exchange in systems where there is no positive charge at nitrogen are subject to acid catalysis (see page 121).

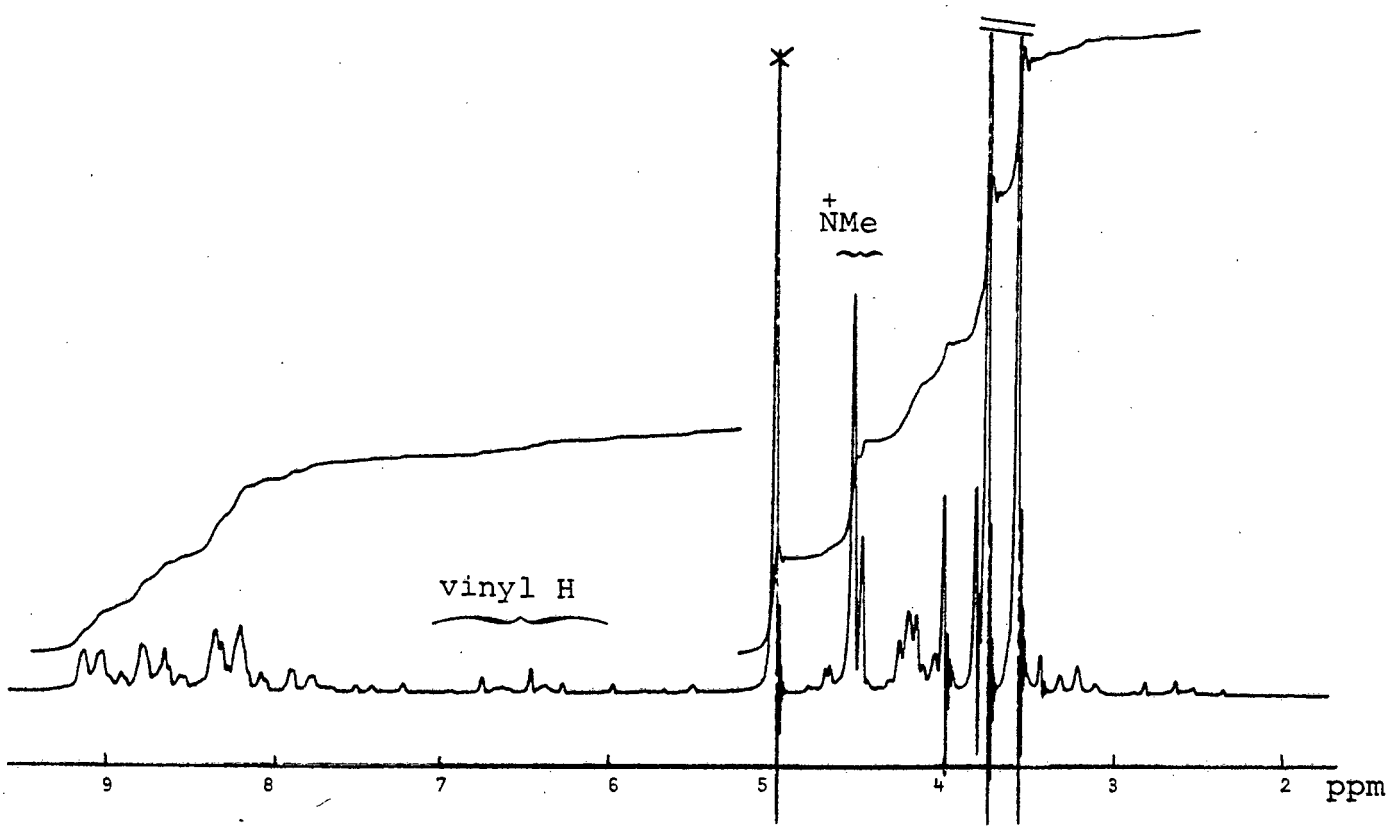
We suspect that base catalysis operates in the elimination reaction. It is not possible at this stage to tell whether the elimination reaction is subject to general or specific base catalysis as we did not carry out any experiments (reactions in buffered solutions) aimed at answering this question. Furthermore, our intention was not to digress to topics far removed from the central theme of methyl transfer.

Before discussing methyl transfer from TMP to [β-(2-pyridylethyl)] acetate, it is of interest to now include the results obtained for

the reaction of TMP with the parent alcohol, β-(2-pyridyl)-ethanol (eq. 4.22). Firstly, although we did not observe the formation of the alcohol in the reaction of the acetate, it cannot be taken as evidence for the absence of hydrolysis, because of possible further reaction of the hydrolysis product. Secondly, the reaction represented by eq. 4.22 would provide us with the values of the chemical shifts for the product $(C_5H_4\overset{+}{N}CH_3)CH_2CH_2OH.DMP^-$.

Figure 4.5 shows the NMR spectrum of the product mixture obtained from refluxing β-(2-pyridyl)-ethanol and TMP in D_2O for 2h.

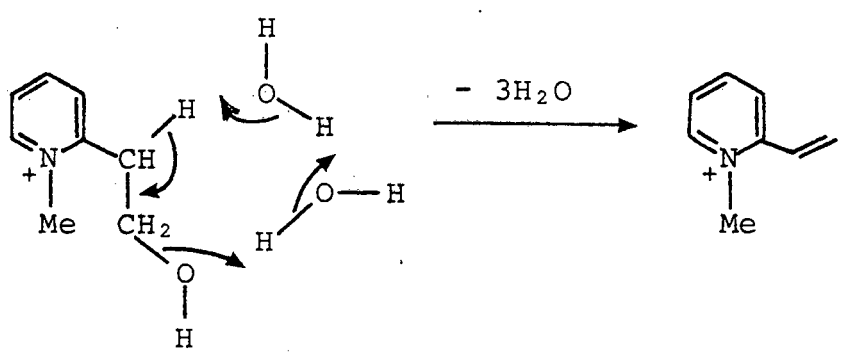
Figure 4.5



Immediately obvious from the spectrum are two sharp singlets at δ4.58 and δ4.52 which are assigned to N-methyl absorptions. Using the amount of TMP consumed as the basis on which to calculate the

percentage N-methylation, there is *ca.* 85% O → N methyl transfer. Also evident from fig. 4.5 are low intensity signals in the vinyl proton absorption range. These in fact account for 14% of the reaction products (this being the lower limit calculated in the absence of H/D exchange) which is quite remarkable as the hydroxide ion, can, without any doubt, be labelled as a "poor" leaving group. (In a recent review by Stirling,[65] no mention is made of the nucleofugality[66] of the hydroxide ion.)

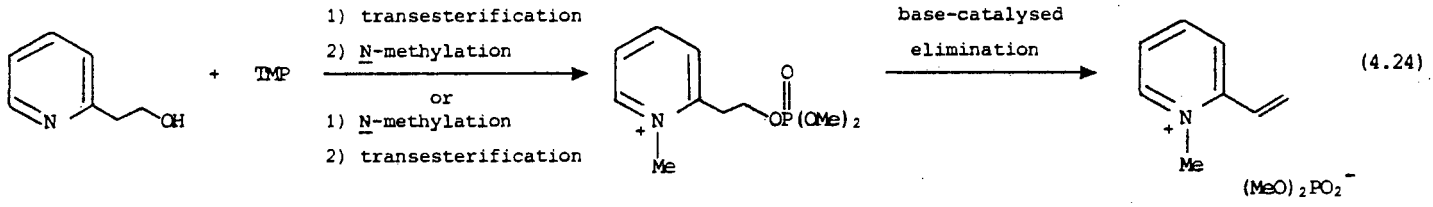
We believe there are only two possible explanations for this observation. Firstly, we postulate that the amphoteric properties of water enable water to function both as a base which accepts the acidic hydrogen atom at the carbon atom β to the hydroxyl group and at the same time to function as an acid in accepting the leaving group, as shown in eq. 4.23 by arbitrarily including two water molecules in the transition state.



(4.23)

It is known[65] for eliminations in the phenylethyl series, that removal of the β-proton and leaving group is concerted. Nucleofugality scales have been shown[67] to be solvent dependent and as water is also the medium for the reaction, the enhanced nucleofugality of the hydroxide ion can possibly be attributed to hydrogen bonding with the solvent. Secondly, refluxing a mixture of β-(2-pyridyl)-ethanol and TMP could result in transesterification and

the product from this reaction could undergo base-catalysed elimination with formation of N-methylated 2-vinylpyridine - see eq. 4.24.



(4.24)

The singlet at δ4.52 would then be a reasonable assignment for the N-methyl absorption of the N-methyl-(2-vinylpyridinium) ion. The intense singlet at δ4.58 more than likely corresponds to the N-methyl absorption of the primary product, i.e. the N-methyl-β-(2-hydroxyethyl)pyridinium ion.

However, as it will soon be seen in the experiments involving [β-(2-pyridylethyl)] acetate, the methylene protons of the product are less easy to account for. The unresolved singlet at δ4.20 could be due to the absorption of the methylene protons and to the hydroxyl group. The absorption of the protons of the second methylene group may be masked by the large doublet from the methyl proton absorption of dimethyl phosphate.

The results from following the reaction at 60°C (system VIb) are more informative and a series of NMR spectra are given in fig. 4.6a-d. H/D exchange at the α-carbon atom to pyridine is

* base = another molecule of substrate - β-(2-pyridyl)-ethanol.

illustrated quite clearly by the change of the NMR signals for both methylene groups of the reaction product. After 24 h (fig. 4.6a) the N-methylation is well advanced (78% based on TMP used). The ^{1}H NMR signals of the methylene groups show that some H/D exchange also took place at the β-position. The triplet for the β-methylene group (δ3.44) has the intensity of only *ca.* 85% of that of the N-methyl group (δ4.44), and the α-methylene group (δ4.05 - 4.22) appears as an overlapping mixture of a triplet and a doublet, the latter resulting from the neighbouring β-CHD group. Spectra presented in figs. 4.6b-d show the completion of the N-methylation (no TMP present), but also the increasing and finally, complete exchange at the β-methylene group. After 245 h (fig. 4.6d), the reaction product exists virtually as the β,β-dideuterated N-methyl derivative, $(C_5H_5NMe)^+CD_2CH_2OH.DMP^-$; the signal at δ3.44 has disappeared almost completely, and that at δ4.15 has been reduced to a singlet. It is worth pointing out that the unreacted one third of the substrate remains in the solution without any noticeable H/D exchange, as indicated by the two undistorted triplets (δ3.04 and δ3.96) of both methylene groups. These results also show the increased ability of the system to exchange when there is a positive charge development at nitrogen.

Having established a few facts about the reactivity of [β-(2-pyridyl-ethyl)] acetate and its parent alcohol, we are now in a better position to deal with the problem of the O → N methyl transfer from trimethyl phosphate. In addition to this, because of the difficulty in interpreting the ^{1}H NMR spectrum of the final reaction products (fig. 4.4) the experiment was repeated under milder conditions (T = 60°C) so that the progress of the reaction could

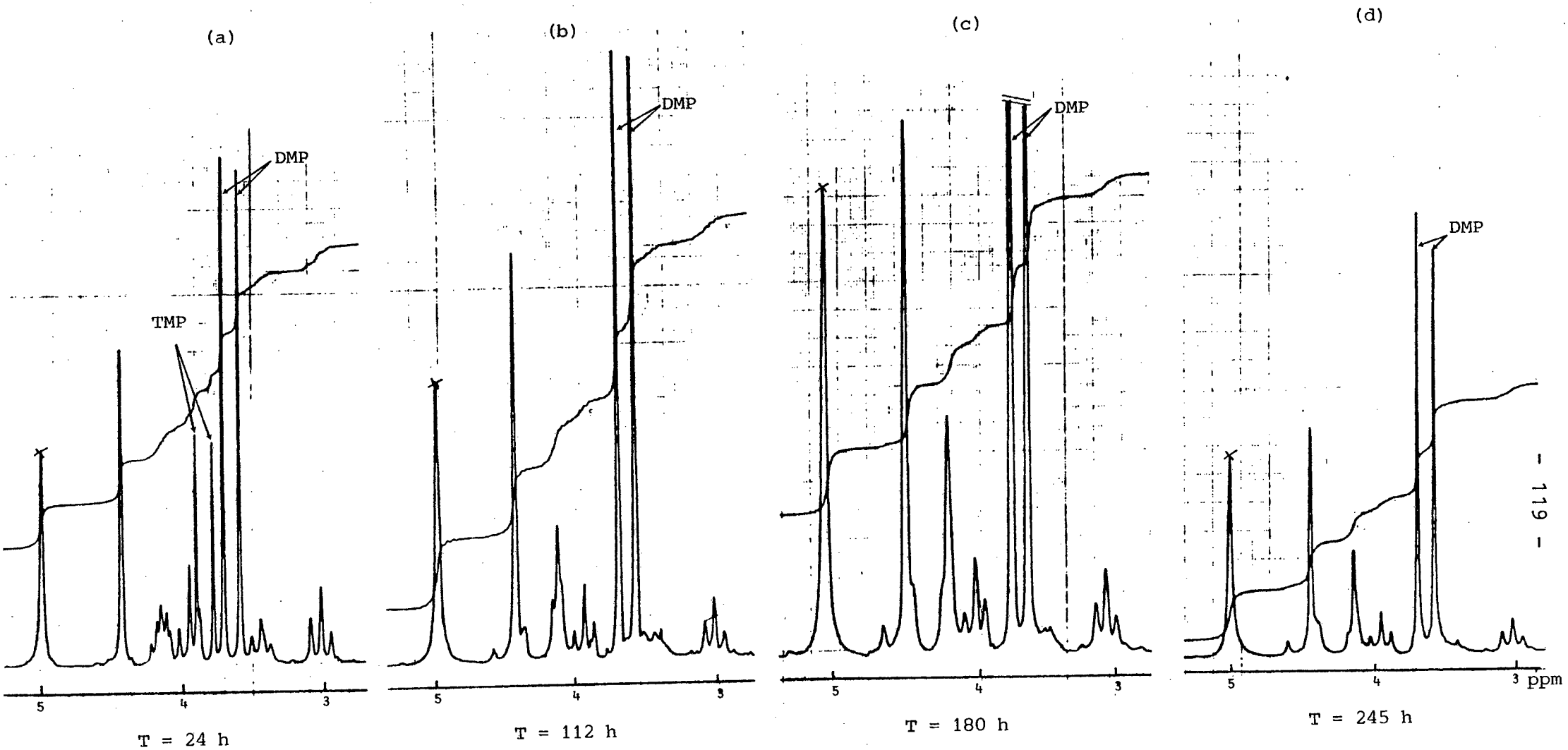


Figure 4.6 A series of ^{1}H NMR spectra illustrating H/D exchange in System VIb

be followed. The changes in the spectrum due to H/D exchange were analogous to those shown in fig. 4.6a-d.

In both systems Va and Vb, although 0.67 mole equivalents of trimethyl phosphate and 1 mole equivalent of pyridine substrate were used, the methylating reagent was still present when all substrate had been used up. This immediately suggested that the substrate was involved in secondary reactions.

Nucleophilic attack of the substrate or of the elimination product (2-vinylpyridine), formed from the substrate, on TMP will result in an N-methyl absorption in the ^{1}H NMR spectrum. At first glance, in both spectra for Va and Vb, it appeared that there were two N-methyl absorptions in the chemical shift range *ca.* δ4.4-5.5. As already mentioned, the downfield shift of the vinyl proton absorptions was also evidence for the pyridyl nitrogen bearing a positive charge. The spectrum obtained from Vb showed that the α-H in 2-vinylpyridinium ion had exchanged to 100% (there were no signals at δ6.6-7.4). This exchange has distorted the H_β and H_γ proton absorptions and we were not able to assign the broad signals between δ5.77-6.63 to neither H_β nor H_γ since the intergration was not especially informative. We suspect that one of the N-methyl singlets could be the result of the N-methylated hydrolysis product which has undergone exchange. Also the fact that after evaporation of any volatile reaction products, an acetyl CH_3 proton absorption remained, indicates that some N-methylated [β-(2-pyridylethyl)] acetate was present. There were no well defined triplets corresponding to the methylene groups of this product and we attribute this to H/D exchange.

The occurrence of an exchange reaction between 'heavy' water and a substance of natural isotopic composition dissolved in it may be detected either by monitoring the deuterium concentrations (of the solvent and/or solute) or by observing changes in spectral data (infrared and/or ^{1}H NMR). In these experiments we have relied entirely on observations from the ^{1}H NMR spectral data and while it would be desirable to check these results by deuterium analysis of the solute and/or solvent, this would not only have necessitated the development of some special analytical methods, but also it would have necessitated the involvement in a study which for the intents and purposes of this thesis, was considered - although very interesting - a side reaction.

The data presented should be interpreted as implying only that under the conditions recorded, exchange reactions at selected positions proceeded to variable degrees. It is of interest to compare the high lability of the protons of [β-(2-pyridylethyl)] acetate with the lack of lability of the protons of 2-pyridyl-methanol and β-(2-pyridyl)-ethanol under theoretically the same conditions of concentration and temperature. It is evident that attention must be paid to both these variables. From our standpoint we propose that traces of acid (formed by the hydrolysis of β-(2-pyridylethyl)] acetate accelerate the exchange of the methylene and vinyl protons in the parent alcohol and the elimination product respectively. However, further experiments would be necessary to test this hypothesis.

There is a wealth of literature describing H/D exchange at the ring positions in heterocyclic compounds. For example, Zoltewicz

that dimethyl-[β-(2-pyridylethyl)] phosphate, because of its

and coworkers[68] have studied rates of H/D exchange of pyridine, pyrimidine, pyridazine and pyrazine in CH_3OD-CH_3ONa at 164.6°C. More recently[59] an H/D exchange study of some heteroaromatics (pyridine, 2-, 3- and 4-methylpyridine and 1,10-phenanthroline) in neutral water at elevated temperatures (180 - 300°C) was undertaken. Despite these and further examples cited in the literature,[56a,61] we did not observe any exchange of the pyridyl ring protons (DSS was used as the internal standard) and we attribute this result to the relatively mild conditions used in our study.

Before concluding, it is worthwhile to note that after 14 months in a refrigerator at *ca.* 8°C, dimethyl-[β-(2-pyridylethyl)] phosphate underwent elimination to the extent of 30% (calculated from ^1H NMR spectral data). In comparison, [β-(2-pyridylethyl)] acetate was stable under the same conditions after 17 months. This result is consistent with either the dimethyl phosphoryloxy substituent being a better leaving group than the acetoxy grouping or the pyridyl nitrogen atom in substrate B being a stronger base than that in substrate F. As in this case, the first proposal counteracts the second, we believe it is the more favourable leaving group ability of the dimethyl phosphoryloxy substituent which promotes the elimination reaction. Support for the leaving ability of a group is manifested in its pKa value, which for dimethyl phosphoric acid and acetic acid are 1.29[69] and 4.75,[18] respectively. Dimethyl-phosphate anion is therefore *ca.* $10^{3.5}$ times a better leaving group than the acetate anion when expressed in terms of pKa values of their conjugate acids.

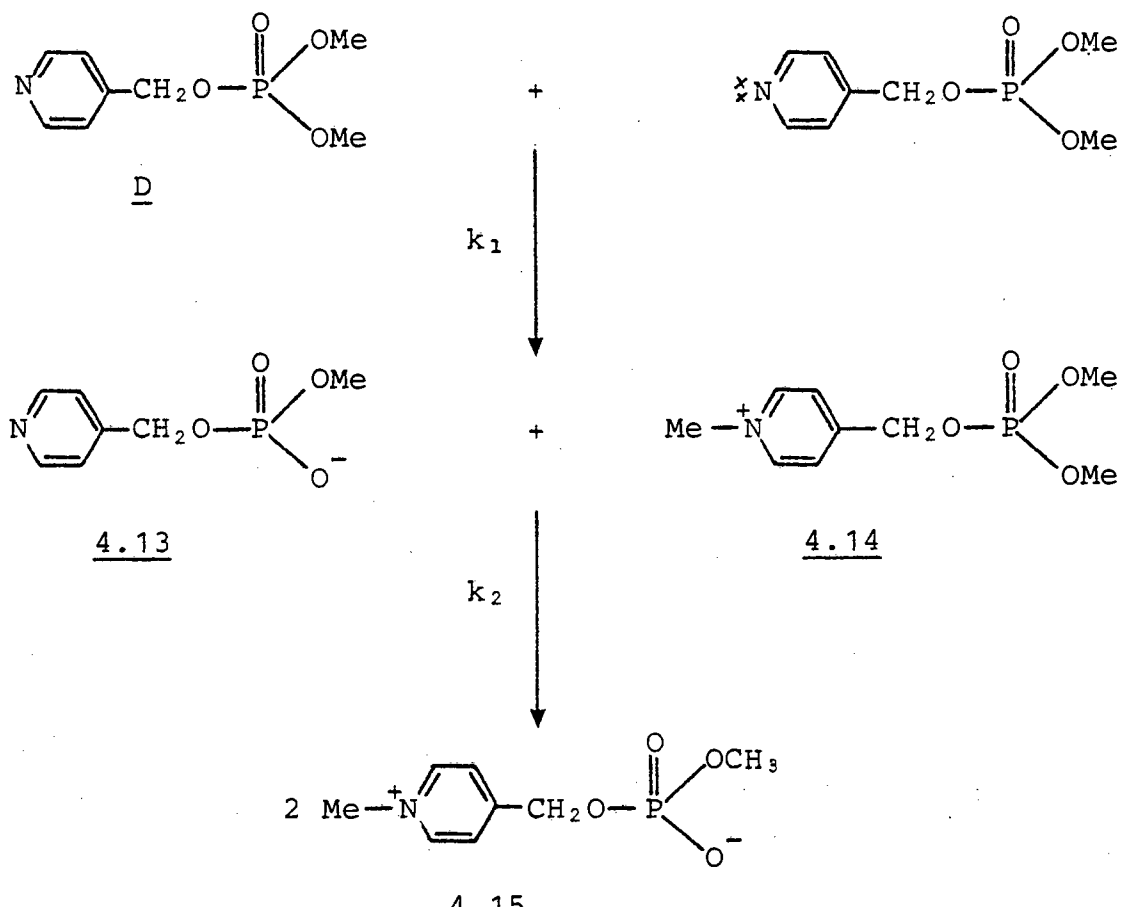
In view of the previous results and discussion, we can conclude that dimethyl-[β-(2-pyridylethyl)] phosphate, because of its

chemical versatility, is not a suitably 'clean' model substrate with which to investigate the O → N methyl transfer.

4.3 A STUDY OF THE N-METHYLATING BEHAVIOUR OF DIMETHYL-(4-PYRIDYL-METHYL) PHOSPHATE, D.

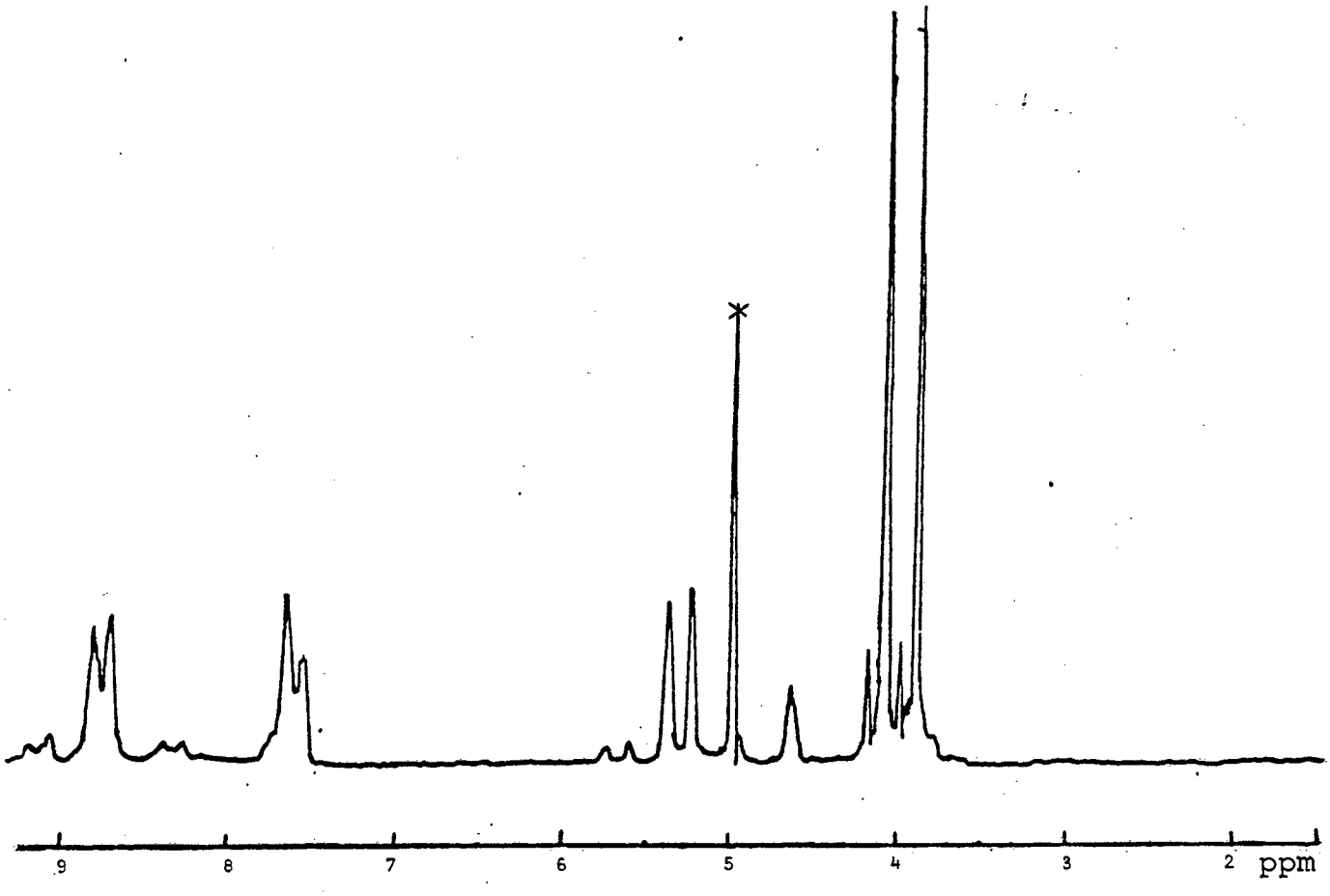
As for compounds A and B, these reactivity studies are intended to establish on a semi-quantitative level, the credibility of the molecular system to undergo methyl transfer from ester oxygen to pyridyl nitrogen. An intramolecular process for the methyl transfer reaction is very unlikely, if not impossible, as the nitrogen is too far removed from the methyl ester phosphate group. It is then conceivable that compound D has the potential for an intermolecular O → N methyl transfer, as shown below in scheme 4.4.

Scheme 4.4



Because of the problems in synthesizing the substrate, only enough pure substrate for one study was obtained. Dimethyl-(4-pyridylmethyl) phosphate kept neat as an oil at 8°C was examined by dissolving samples in D_2O and recording their ^1H NMR spectra. A signal assigned to the N-methyl group was seen to appear at δ4.65. After 22 days, approximately 14% of D had become methylated at the pyridyl nitrogen atom (see fig. 4.7).

Figure 4.7 ^1H NMR spectrum of dimethyl-(4-pyridylmethyl) phosphate and its N-methylated salt.



This is in contrast to the 2-pyridylmethyl analogue, A, which is stable indefinitely in neat form. The doublets for the O-methyl protons of the O-demethylated and N-methylated intermediates (4.13 and 4.14) were observed in the NMR spectrum at δ3.78 and δ4.05,

respectively. The postulated final product - the zwitterion 4.15 was not observed because either if k_1 and k_2 are comparable or if $k_2 < k_1$, it would have been present in too small an amount to be detected by ^1H NMR spectroscopy, and/or even if $k_2 > k_1$, the absorptions would be masked by the substrate.

Because of the synthetic difficulties encountered, no further attempt to prepare analytically pure dimethyl-(4-pyridylmethyl) phosphate was made. We conclude simply that dimethyl-(4-pyridylmethyl) phosphate exhibited marked intermolecular methyl transfer compared to its 2-pyridyl substituted isomers.

4.4 ALKYLATING PROPERTIES OF PHOSPHATE ESTERS. OXYGEN → NITROGEN METHYL TRANSFER IN DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE[70]

Although in ch. 4.1.2 preliminary evidence for the formation of the ionic intermediates $\underline{AI}^+$ and $\underline{AI}^-$, followed by their disappearance, demonstrated qualitatively some bimolecular nature of the isomerisation, we were not in a position to evaluate the extent of this mechanism or to unequivocally state whether any intramolecular catalysis takes place. It is kinetic measurements, and in particular the effect of substrate concentration on the reaction rate, which provide quantitative evidence for the intermolecular mechanism. ^1H, ^{13}C and ^{31}P NMR spectroscopy were used as tools for this investigation.

4.4.1 A ^1H NMR STUDY ON THE EFFECT OF CONCENTRATION ON THE RATE OF O → N METHYL TRANSFER - INTER vs INTRAMOLECULAR REACTION

Four solutions of known concentration (0.55 M, 1.17 M, 1.50 M and 1.97 M) of the substrate in D_2O, were prepared and the rate of reaction at 60°C of these four different concentrations was monitored by ^1H NMR spectroscopy. This involved periodically withdrawing the NMR tube from the waterbath, placing it in an ice-waterbath (to arrest the progress of the reaction), recording the ^1H NMR spectrum of the sample, and returning the tube to the thermostatted bath. The progress of the reaction was determined by following the rate of substrate disappearance. The doublet for the methylene group absorption at δ5.25 was chosen as the absorption from which to calculate the rate of the reaction, as there was the least overlapping of substrate/intermediate and/or /product proton

absorptions at this chemical shift position. The percentage reaction was then simply:-

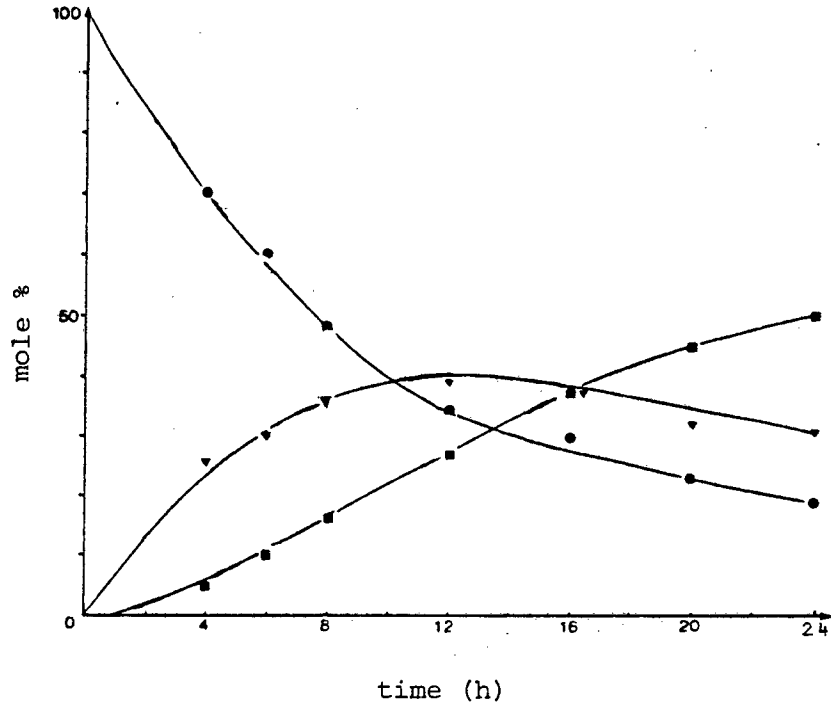
$$= \frac{\text{intergrated area of the doublet for the substrate methylene protons x 100}}{\text{total intergrated area for the methylene signals}}$$

When the 1.97 M solution of A in D_2O was kept at 60°C and the reaction progress examined periodically by ^1H NMR spectroscopy, changes in concentrations of individual species present with time gave a plot typical for systems involving exponential decay of the substrate, transient formation of intermediates and delayed product formation (see fig. 4.8).

Figure 4.8

Reaction of A in D_2O at 60°C: Composition of the mixture at different times.

- ● A
- ■ 4.1
- ▼ $AI^+ + AI^-$



The results are interpreted considering both extreme reaction mechanisms - either a unimolecular reaction or a bimolecular reaction, and are given in tables 4.3 and 4.4. Plots of

$\ln(\frac{a_o}{a_o - x_t})$ and $\frac{x_t}{a_o(a_o - x_t)}$ (where a_o = initial concentration of substrate x_t = concentration of substrate at time t) versus time, as required by the 1st- and 2nd-order rate laws, respectively, are shown in figs. 4.9 - 4.12. In all cases the graphs show that not only does the plot for the 1st-order reaction deviate more from linearity than the plot for the bimolecular reaction, but also all 1st-order plots show distinct curvature in a direction expected for a more rapid decrease of reaction rate with a decrease in substrate concentration. The correlation coefficient, r,* provides a direct measure of the linearity of the plot and as the correlation coefficients for the individual k_1 values are slightly lower than those of the k_2 values, the isomerisation is described much better by the 2nd-order than by the 1st-order rate law. But the most obvious result from table 4.3 is the effect of variations in a_o values on the individual rate constants. The 3.6 fold decrease in the initial substrate concentration results in a drop of the k_1 value to only 56% of its highest value. The k_2 values on the other hand, show a random scatter due to the inaccuracy of the kinetic technique employed. As a further check for the 2nd-order kinetics, the half-lives were determined for the series of different initial concentrations, and a plot of these values against the reciprocal of the initial concentrations is shown in fig. 4.13. The 2nd-order rate coefficient as determined from the slope of this straight line is 3.77×10^{-5} $M^{-1}s^{-1}$ and it agrees well with the average value obtained from the kinetic runs. The

*All correlation coefficients obtained by a least squares linear regression.

correlation coefficient of 0.9989 enables us to conclude that the reaction is bimolecular with no evidence for a contribution from the unimolecular pathway.

Table 4.3 Rates of the O→N methyl transfer in dimethyl-(2-pyridyl-methyl) phosphate; D_2O, 60°C

a_o (M)	$10^5 k_1$ (s^{-1})	r	$10^5 k_2$ ($M^{-1}s^{-1}$)	r
1.97	1.83	0.9888	2.73	0.9984
1.50	1.80	0.9924	3.08	0.9987
1.17	1.53	0.9878	3.05	0.9924
0.55	1.03	0.9841	3.43	0.9958
av.	1.55 ± 0.37	0.9883 ± 0.0035	3.07 ± 0.29	0.9963 ± 0.0029

The disturbance due to secondary hydrolysis of the substrate in the time taken for the experimental measurements is negligible. The hydrolysis of trimethyl phosphate was independently investigated at 60°C and illustrates this clearly. The value of the pseudo-first order rate coefficient, obtained from 12 readings over 28 days, was $3.98 \times 10^{-7} s^{-1}$.* After 24 hours only approximately 8.5% hydrolysis had occurred which if corrected statistically for the number of methyl groups present, would give approximately 5.5% hydrolysis of substrate. These results are shown in table 4.5 and the 1st-order kinetic plot for the hydrolysis of trimethyl phosphate is given in fig. 4.14.

*A recorded pseudo first order rate constant for the hydrolysis of trimethyl phosphate in H_2O at 80°C is reported as $3.36 \times 10^{-4} s^{-1}$.[17]

Table 4.4 Kinetic results for 1.97 M, 1.50 M and 0.55 M solutions of dimethyl-(2-pyridylmethyl) phosphate at 60°C

Concentration	Time (hours)	% reaction[a]	$\ln\frac{a_o}{a_o-x}$ [b]	$\frac{x}{a_o(a_o-x)}$
1.97 M	4	29.9	0.356	0.217
	6	40.1	0.513	0.341
	8	51.8	0.729	0.545
	12	66.0	1.079	0.985
	16	72.0	1.279	1.303
	20	77.2	1.477	1.708
	24	81.2	1.672	2.192
$k_1 = 1.83 \times 10^{-5} s^{-1}$	(r = 0.9888)	$k_2 = 2.73 \times 10^{-5} M^{-1} s^{-1}$		(r = 0.9984)
1.50 M	4	20.6	0.223	0.167
	6	33.1	0.401	0.330
	8	45.0	0.598	0.545
	12	58.0	0.868	0.921
	16	68.1	1.143	1.423
	20	74.0	1.347	1.897
	24	78.0	1.514	2.364
$k_1 = 1.80 \times 10^{-5} s^{-1}$	(r = 0.9924)	$k_2 = 3.08 \times 10^{-5} M^{-1} s^{-1}$		(r = 0.9987)

cont./

cont.

1.17 M	4	19.0	0.211	0.200
	6	30.0	0.357	0.366
	8	44.0	0.580	0.672
	12	56.2	0.825	1.096
	16	62.5	0.981	1.425
	20	67.4	1.121	1.767
	24	74.7	1.374	2.524
$k_1 = 1.53 \times 10^{-5} s^{-1}$	(r = 0.9878)	$k_2 = 3.05 \times 10^{-5} M^{-1} s^{-1}$		(r = 0.9924)
0.55 M	4	17.0	0.186	0.372
	6	26.2	0.304	0.646
	8	38.0	0.478	1.114
	12	45.0	0.598	1.485
	16	50.8	0.709	1.878
	20	57.4	0.853	2.449
	24	61.5	0.955	2.906
$k_1 = 1.03 \times 10^{-5} s^{-1}$	(r = 0.9841)	$k_2 = 3.43 \times 10^{-5} M^{-1} s^{-1}$		(r = 0.9958)

[a] % reaction is taken as the % of substrate used.

[b] $x = \frac{\%\ \text{substrate used}}{100} \times a_o$

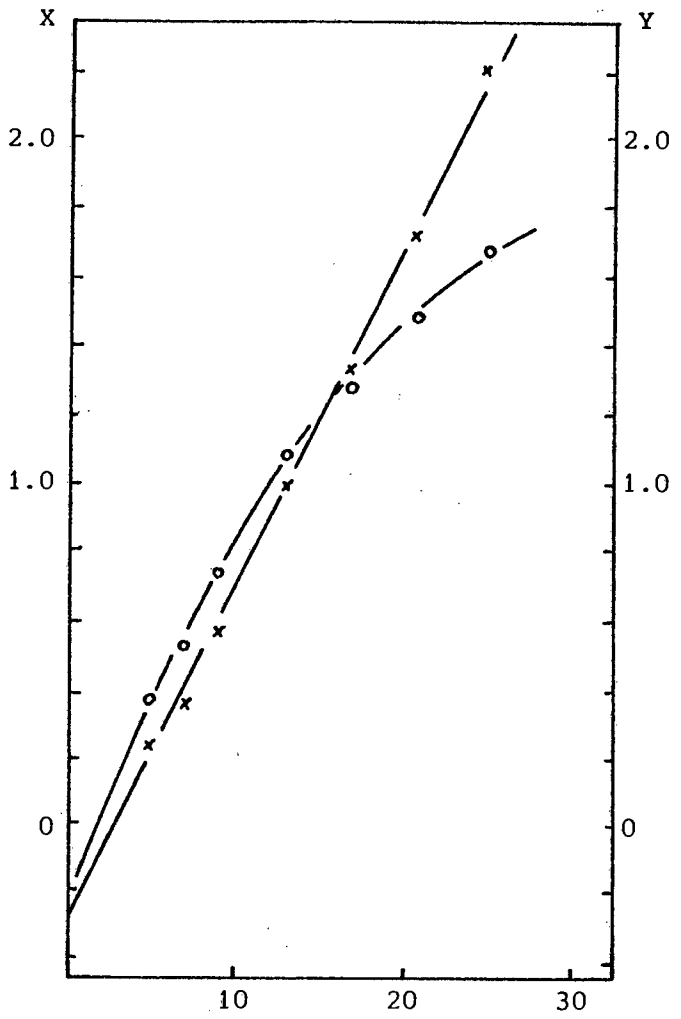
Table 4.5 Kinetic Results for the hydrolysis of trimethyl phosphate (60°C)

Concentration	Time (hours)	% reaction	$\ln\frac{a_o}{a_o-x}$
1.95 M	17	4.8	0.049
	24	8.6	0.090
	64	12.7	0.136
	135	22.0	0.249
	231	31.9	0.384
	280	38.0	0.478
	311	39.8	0.508
	398	47.8	0.654
	444	51.6	0.734
	567	56.5	0.833
	662	62.2	0.973

$k_1 = 3.98 \times 10^{-7} s^{-1}$ (r = 0.9967)

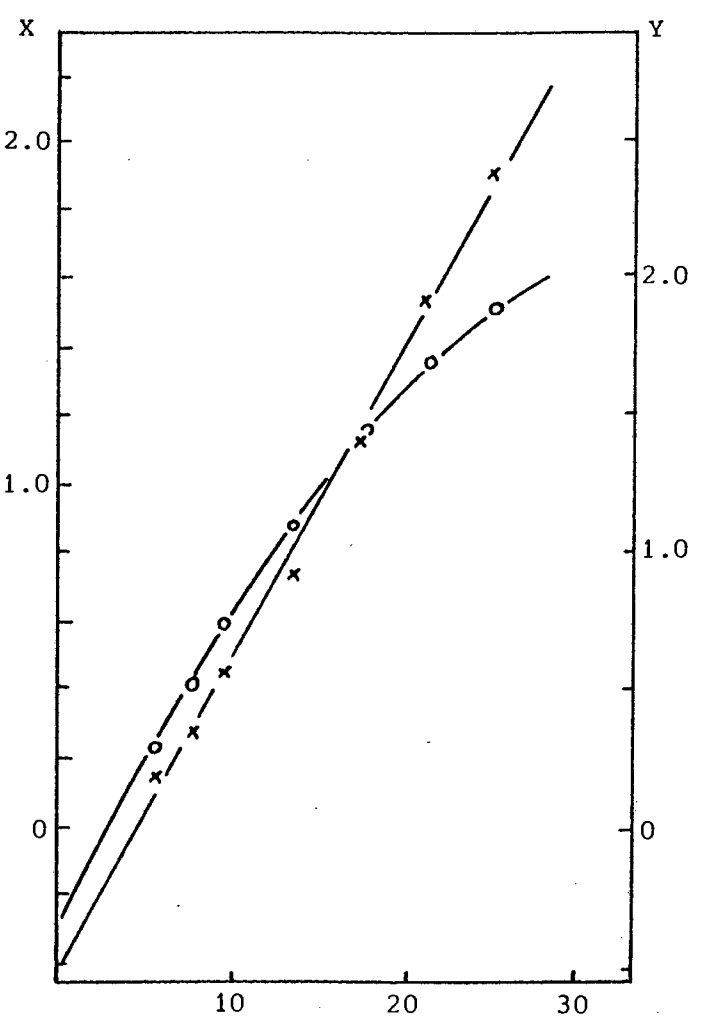
First- (o) and second-order (×) kinetic plots for substrate (A) disappearance in D_2O at 60°C

Figure 4.9 a_o = 1.97 M



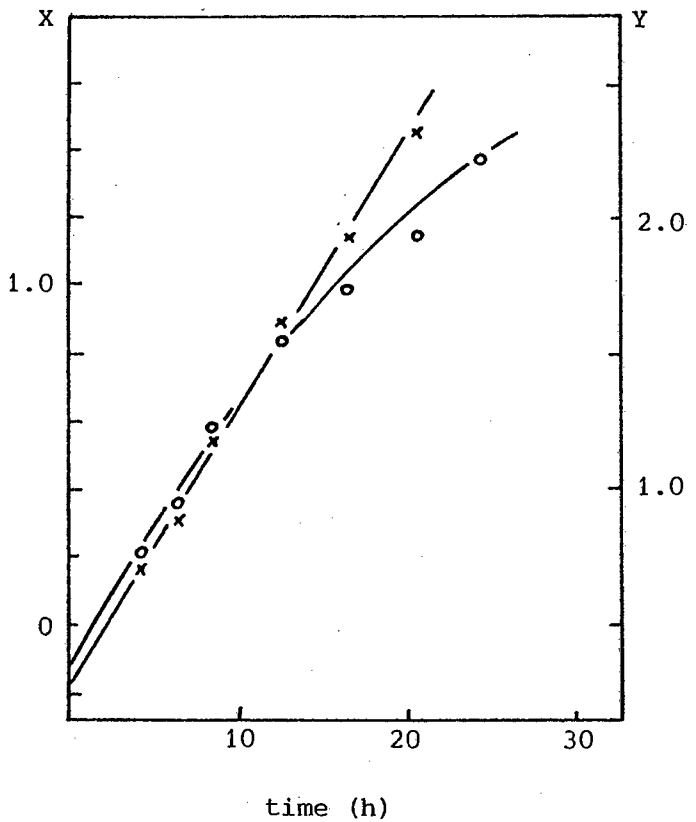
$$X = \frac{x}{a_o(a_o-x)}, \qquad Y = \ell n\left(\frac{a_o}{a_o-x}\right)$$

Figure 4.10 a_o = 1.50 M



First- (o) and second-order (×) kinetic plots for substrate (A) disappearance in D_2O at 60°C

Figure 4.11 a_o = 1.17 M



$$X = \frac{x}{a_o(a_o-x)} \qquad Y = \ell n \left(\frac{a_o}{a_o-x}\right)$$

Figure 4.12 a_o = 0.55 M

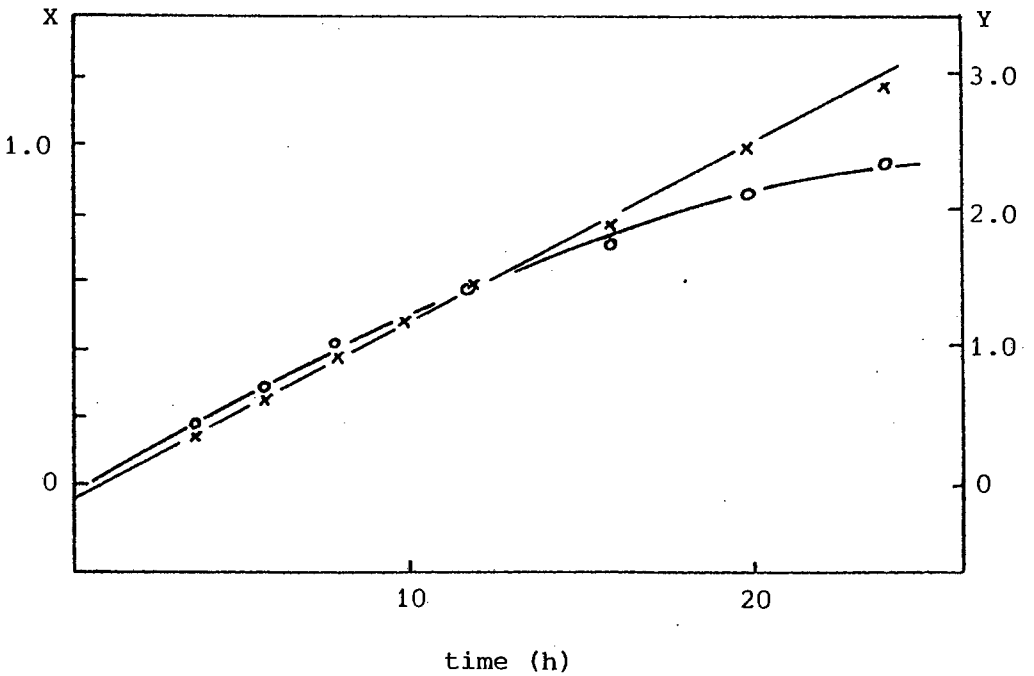


Figure 4.13 A plot of $t_{\frac{1}{2}}$ versus $^{1}/a_{o}$

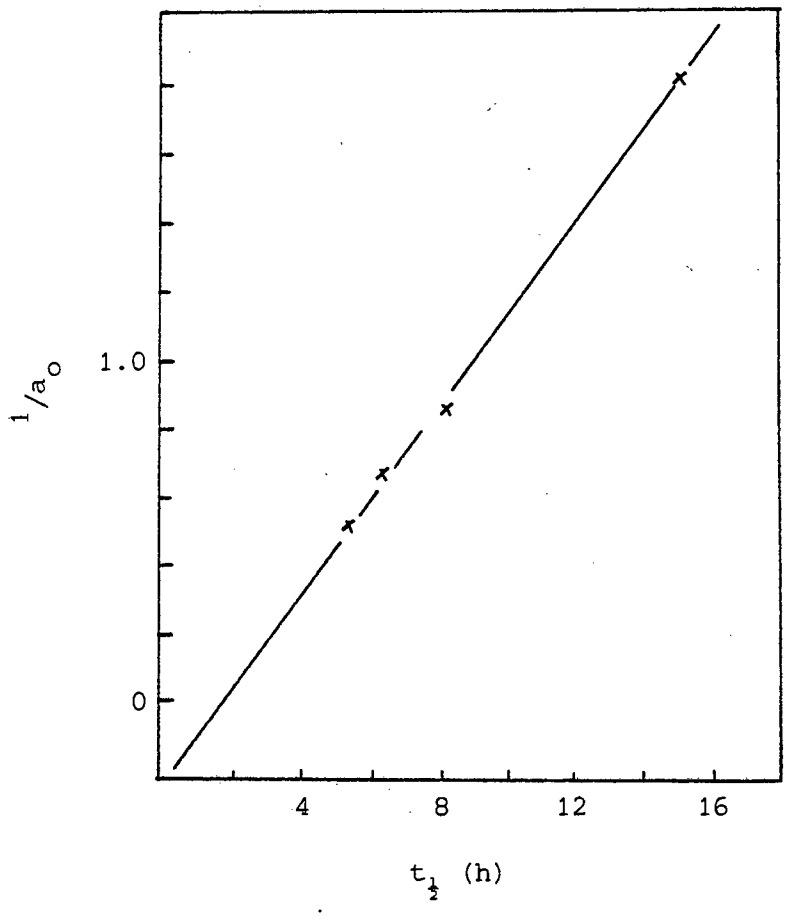
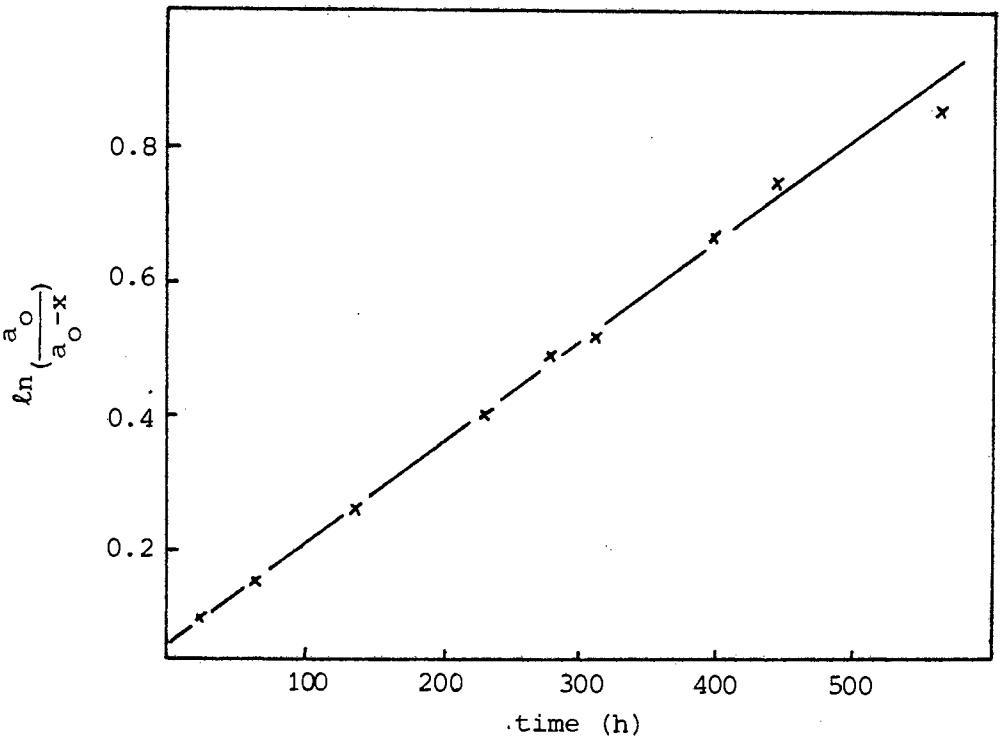


Figure 4.14 First-order kinetic plot for hydrolysis of TMP at 60°C



4.4.2 INVESTIGATION OF THE O → N METHYL TRANSFER REACTION MECHANISM BY ^{13}C NMR SPECTROSCOPY

Although the ^{1}H NMR spectral features for the isomerisation of dimethyl-(2-pyridylmethyl) phosphate have been unambiguously assigned and characterized, the difference in ^{1}H chemical shifts of the individual species in combination with the additional complications produced by proton-proton and phosphorus-proton spin-spin coupling, makes the spectra far from simple. The ^{13}C NMR spectrum on the other hand, shows individual resonances for each carbon generally with well resolved phosphorus-carbon couplings, which in the present case is particularly advantageous as we are primarily concerned with how a specific carbon centre has changed its chemical environment during the course of the reaction. Another asset offered by ^{13}C NMR is the sensitivity of both the chemical shift and the coupling constants to structural change. The carbon chemical shift range is of the order of 200 ppm compared to the 10 - 15 ppm range for the proton and effectively this means that it is easier to distinguish molecules of similar but different constitution.

As the literature concerned with ^{13}C NMR of phosphate triesters is relatively sparse, we were interested in using the information gained from a fully coupled spectrum of A to make a complete assignment of the chemical shifts in a fully decoupled spectrum. In addition to this, we realized the potential of ^{13}C NMR spectroscopy for obtaining quantitative results for the isomerisation reaction. At the present time, the number of published examples of mechanistic studies by ^{13}C NMR is small[71] and besides the complete kinetic analysis of the acetolysis of p-anisylethyl tosylates by ^{13}C NMR,[72] a literature search reveals that ^{13}C NMR spectroscopy

is not used very frequently, without the aid of other methods for the determination of reaction kinetics.

The problem encountered in ^{13}C NMR spectroscopy when one attempts to obtain kinetic results, is that the simple relation between signal intensity and the number of nuclei does not hold because of the nuclear Overhauser enhancement, which itself depends on the nature and environment of a specific carbon so that the enhancement may be variable for carbons in the same molecule. In order to obtain a correlation between the intergrated peak areas and the number of carbon nuclei in each peak, the T_1 values* should ideally be obtained. However, by waiting a long enough time between pulses (through trial and error and some insight), one can attain a situation whereby the peak heights are in fact a quantitative representation of the number of C atoms present. Another obstacle to overcome when using ^{13}C NMR for kinetic analysis arises from the low natural abundance (*ca.* 1%) and the low sensitivity (*ca.* 1/60 that of a proton) of ^{13}C which necessitates the use of concentrated samples. However, having finally established a relatively trouble-free route to the synthesis of A, this problem became quite trivial and the kinetic results could be obtained in a reasonable period of time.

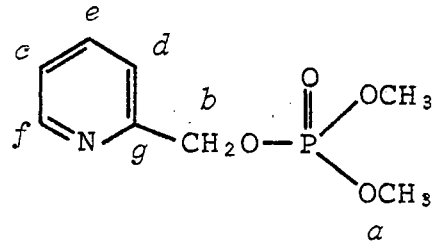
In dimethyl-(2-pyridylmethyl) phosphate any one of the eight carbon atom signals (with the exception of the 'quarternary' or unprotonated carbon atom - labelled *g* in structure 4.16) could be used to

*Spin-lattice relaxation times. It normally takes *ca.* 5 x T_1 to restore the Boltzman distribution to >99%.

follow the reaction. This is because quantitatively meaningful intergrals (to within ± 5%) of these ^{13}C absorptions could be obtained by using 40° pulses followed by a pulse delay of 6 seconds during which time the Broad Band decoupler was gated 'off'. For comparison with the ^{1}H NMR kinetic results we monitored the methylene group absorption. This signal is also the most separated from the absorptions of intermediates and/or products. The reaction was followed at 60°C but the NMR data was collected at 25°C so to minimize any change along the reaction pathway during the data acquisition. To ensure a good signal to noise ratio, a concentrated solution (2.0254 M) of the substrate was used and typically 1 000 scans were collected taking < 1.8 h.

RESULTS AND DISCUSSION

The nomenclature for the carbon atoms is shown in structure 4.16.



4.16

The chemical shift values for the substrate (A), intermediates (AI^+ and AI^-) and product (4.1) are reported in table 4.6. The initial ring assignments were based on ring assignments of 2-ethyl pyridine.[73] The shielding and deshielding effects of *c*, *d*, *e*, *f* and *g* upon N-methylation are in accordance with those observed upon N-methylation in pyridine.[74] Carbon-proton and carbon-phosphorus coupling constants for the substrate and product are listed in

tables 4.7a and 4.7b respectively. From the multiplicities of the signals in the fully coupled spectra of the substrate and the product, it is possible to assign the sharp singlets in the decoupled spectra (see figs. 4.15 and 4.16, respectively).

As in the ^{1}H NMR spectra, the isomerisation of A results in shifts of the signals of the individual atoms. For example, the O-methyl and the methylene carbon atoms in the product 4.1 gave rise to signals shifted upfield (2.1 and 7.1 ppm, respectively), relative to the corresponding signals in A, while the intermediate formation of AI^+ can be demonstrated by the transient appearance of additional signals such as that of the CH_3 ester group shifted 0.7 ppm downfield, and the CH_2 group shifted 5.3 ppm upfield, relative to A. The appearance of a new signal, for the $\overset{+}{N}$-CH_3 group in 4.1 (45.7 ppm), is preceded by the transient formation of a signal at 46.2 ppm - the $\overset{+}{N}$-Me absorption of AI^+ (fig. 4.17).

The kinetic results are collected in table 4.8 and the 2nd-order kinetic plot is illustrated in fig. 4.18. The obtained value of $k_2 = 3.10 \times 10^{-5}\ M^{-1}\ s^{-1}$ ($r = 0.9910$) is in excellent agreement with the value determined by means of ^{1}H NMR spectroscopy and is further illustrated in fig. 4.19 where the plot of the concentration of substrate, product and reaction intermediates as a function of time (based on the intensity of the methylene signals) for the ^{13}C NMR spectra of the mixture almost superimposes the plot obtained by ^{1}H NMR spectroscopy. This result not only provides support for the intermolecular mechanism of the methyl transfer but also illustrates that ^{13}C NMR spectroscopy can be successfully used for measuring the rate of reactions of this type.

Table 4.6 ^{13}C NMR Chemical Shifts Relative to TMS (in ppm)[a]

Carbon atom	Substrate	Product	AI^+	AI^-	Chemical shift of product relative to substrate[b]
a	55.9	53.8	56.6	53.8	-2
b	70.1	63.0	64.8	67.2	-7
c	123.4	127.5	123.4 124.1 124.9	[c]	+4.5
d	125.4		128.2 128.6	[c]	+2
e	139.3	146.7	141.5 147.5	[c]	+7
f	149.7	147.3	154.8	[c]	-2.5
g	154.8	153.9	156.2		-1
$\overset{+}{N}-CH_3$		45.7	46.2		

[a]Dioxane was used as the internal standard and the chemical shift relative to TMS was calculated using δ = 67.4 for dioxane relative to TMS.[71]

[b]A positive value indicates a shift downfield.

[c]These 8 values correspond to the *c*, *d*, *e* and *f* protons of the intermediates. Unambiguous assignment of the signals was not attempted.

Table 4.7a Proton-Carbon and Phosphorus-Carbon Coupling Constants in dimethyl-(2-pyridylmethyl) phosphate.[a]

Atom types	H-C Coupling Constants (Hz)	P-C Coupling Constants (Hz)
$>\overset{\|\|}{P}-O-CH_3$	$^1J_{C,H} = 150$	$^2J_{C,P} = 6$
$>\overset{\|\|}{P}-O-CH_2-$	$^1J_{C,H} = 151$	$^2J_{C,P} = 6$
c	$^1J_{C,H} = 165$	3.5 - 4
d	$^1J_{C,H} = 165$	7
e	$^1J_{C,H} = 165$	6
f	$^1J_{C,H} = 182$	3 - 4

Table 4.7b Proton-Carbon and Phosphorus-Carbon Coupling Constants in methyl-[2-(N-methylpyridinium)methyl] phosphate.[a]

Atom types	H-C Coupling Constants (Hz)	P-C Coupling Constants (Hz)
$>\overset{\|\|}{P}-O-CH_3$	$^1J_{C,H} = 147$	$^2J_{C,P} = 6$
$>\overset{\|\|}{P}-O-CH_2-$	$^1J_{C,H} = 150$	
$\overset{+}{N}-CH_3$	$^1J_{C,H} = 145$	4
c, *d*	$^1J_{C,H} = 176$	6
e	$^1J_{C,H} = 174$	6

[a]See Appendix 1.

Table 4.8 Results of ^{13}C NMR Kinetic Study (a_o = 2.0254 M).

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.5	20.3	0.126
4.5	32.0	0.232
6.0	46.3	0.573
8.0	56.5	0.641
11.0	66.7	0.989
14.0	72.8	1.322
15.0	76.0	1.564

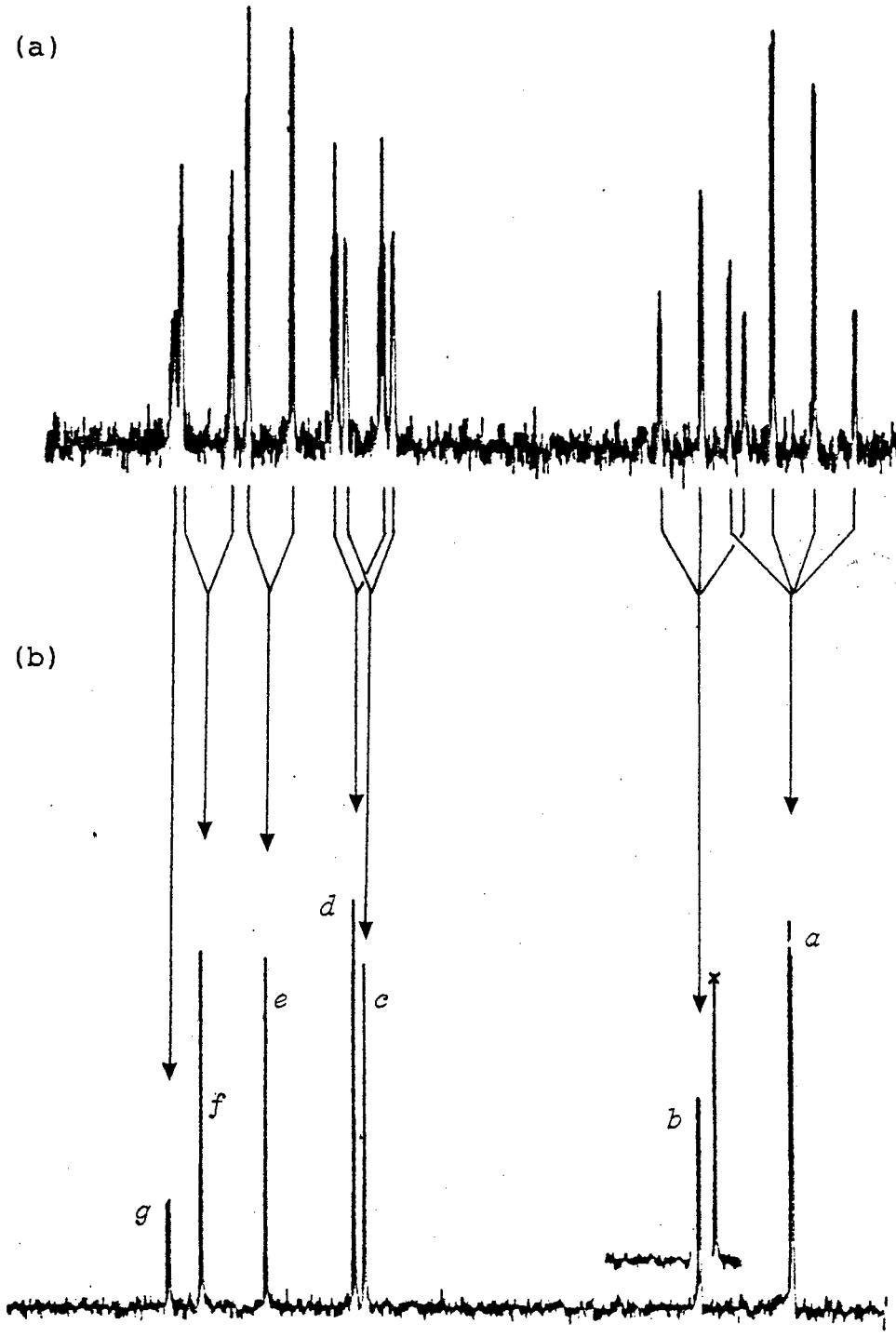


Figure 4.15 ^{13}C NMR spectra of dimethyl-(2-pyridylmethyl) phosphate. (See 4.16 for nomenclature for carbon atoms)

(a) Fully coupled spectrum

(b) Decoupled spectrum

x external standard (dioxane)

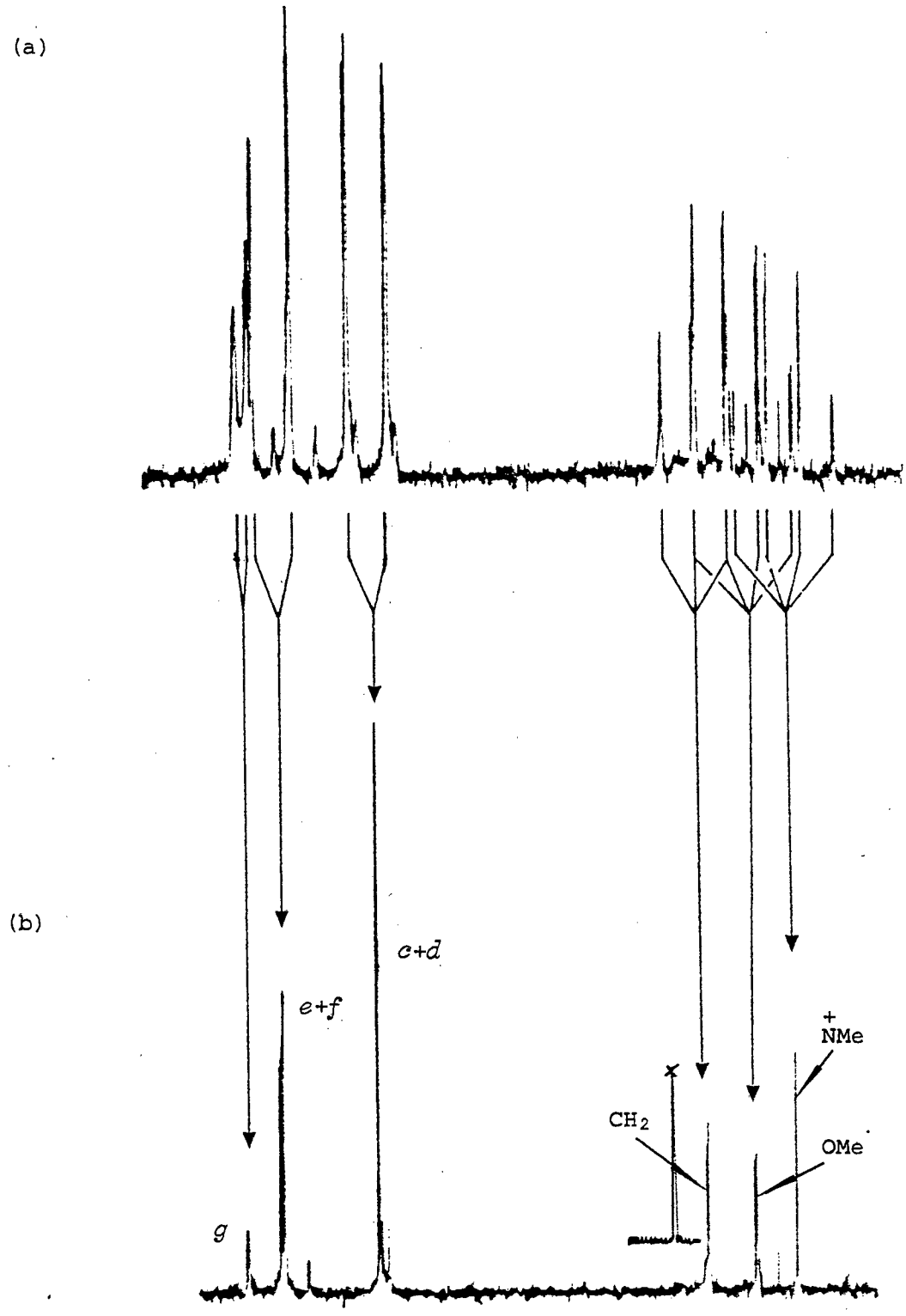


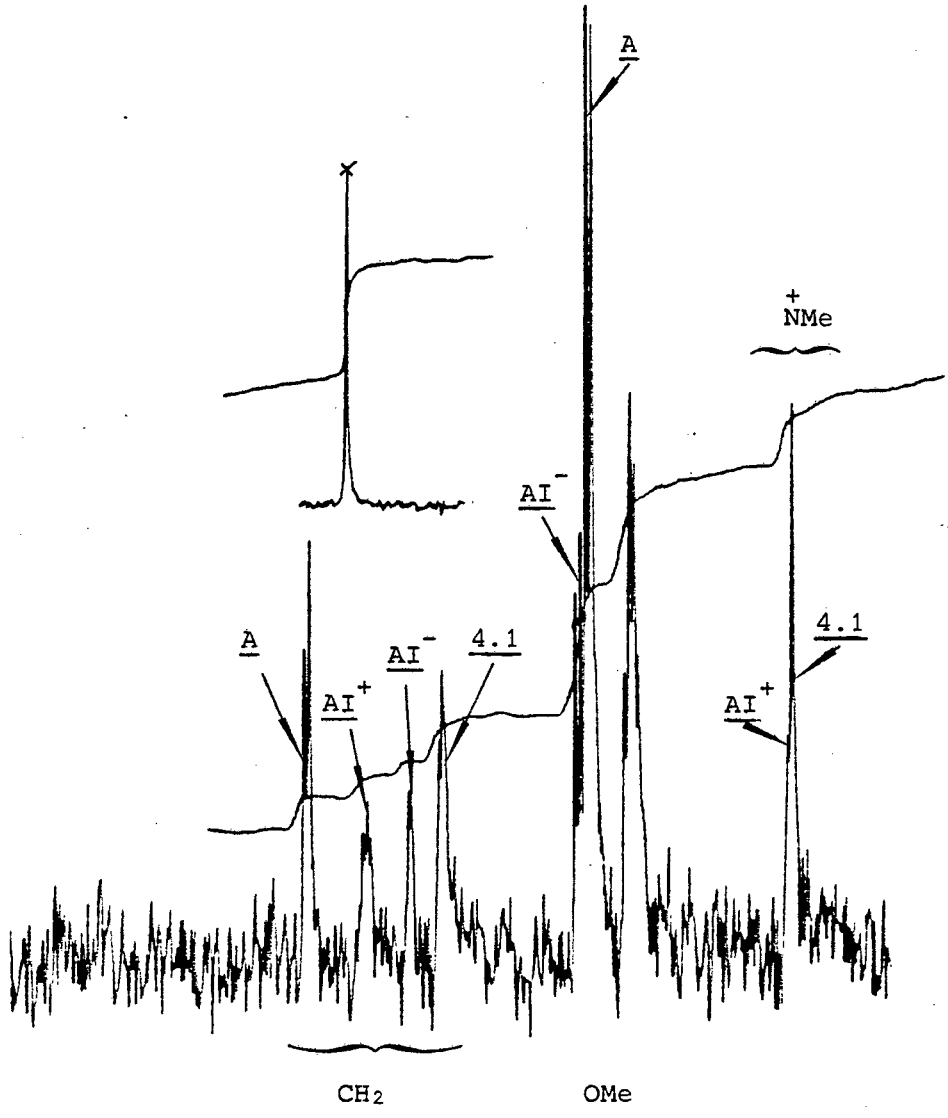
Figure 4.16 ^{13}C NMR spectra of 4.1. Nomenclature for carbon ring atoms is analogous to 4.16.

(a) Fully coupled spectrum

(b) Decoupled spectrum

x External standard (dioxane)

Figure 4.17 ^{13}C NMR spectrum illustrating the species present during the isomerisation of dimethyl-(2-pryidylmethyl) phosphate, A.



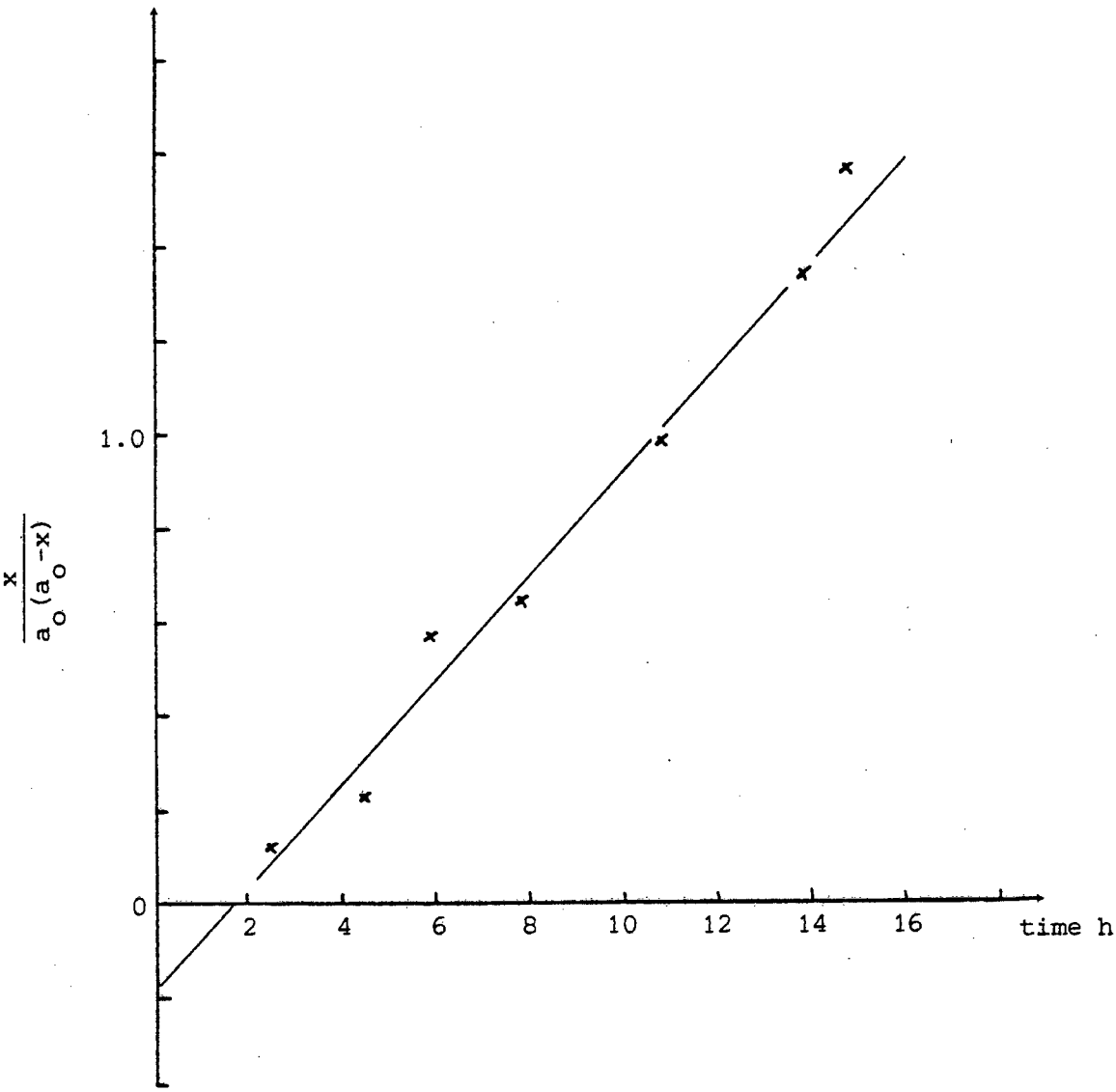


Figure 4.18 Second-order kinetic plot for substrate (A) disappearance in D_2O at 60°C, obtained using ^{13}C NMR spectroscopy (a_o = 2.03 M)

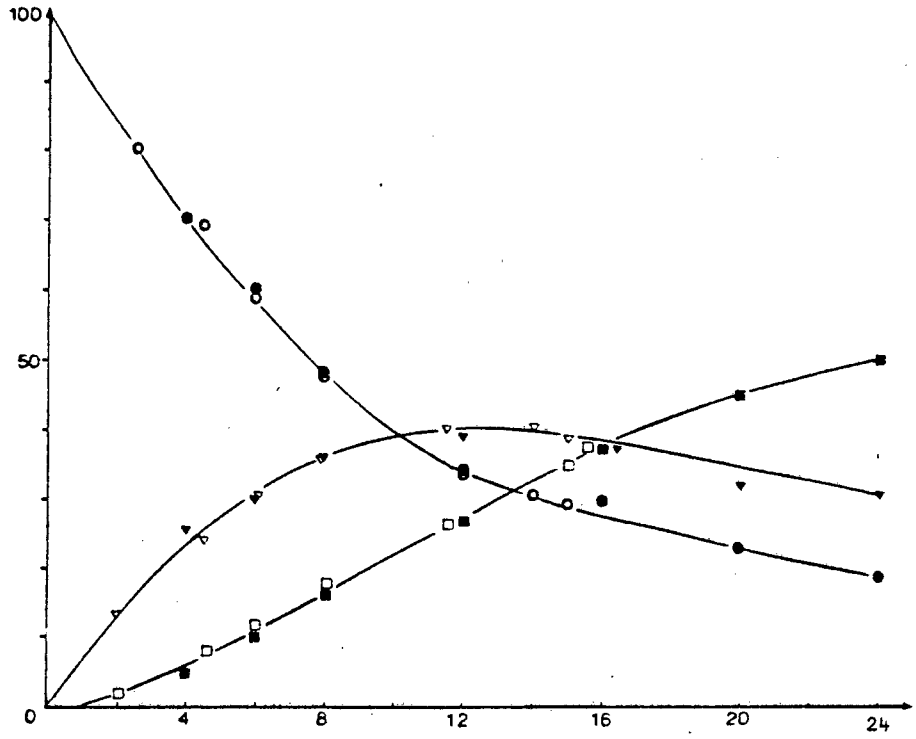


Figure 4.19 Reaction of A in D_2O at 60°C showing the composition of the mixture at different times. Open and full circles correspond to data obtained by ^{13}C and ^{1}H NMR analysis respectively.

o, • A

□, ■ 4.1

∇, ▼ $AI^+ + AI^-$

4.4.3 ^{31}P NMR SPECTROSCOPY AS A TOOL FOR INVESTIGATION OF O→N METHYL TRANSFER

A third possible approach by which to investigate the isomerisation of A → 4.1 and to observe the participation of the intermediates (AI^+ and AI^-) could be based on ^{31}P NMR spectroscopy. Initially it was thought that ^{31}P NMR would be unambiguous for the characterization of each type of phosphorus species present and would offer the most attractive route to the study of the nitrogen→methyl interaction. The ^{31}P NMR spectrum of A shows the expected single signal in the presence of broad band ^1H decoupling (fig. 4.20a) and in fact it is trivial in its simplicity. Over and above this, although ^{31}P has a sensitivity $^1/_6$ that of ^1H, ^{31}P is 100% naturally abundant, large sample tubes can be used and spin-decoupling techniques can be applied to collapse complex spectra resulting from coupling with other magnetically active nuclei in the molecule. Practically, therefore, it is possible to offset to some extent the low sensitivity.

The reaction, however, could only be followed qualitatively by this method, because as the isomerisation progressed, the substrate's signal (-9.26 ppm) was initially replaced by an upfield signal at δ -15.03 (probably the absorption of the anionic intermediate AI^-), which subsequently gave way to the signal of the product 4.1 (-12.85 ppm). The change in the ^{31}P NMR as the reaction progressed is shown in fig. 4.20b-f.

Although P^{III} compounds cover a chemical shift range of 500 ppm, P^{IV} compounds have a chemical shift range of 100 ppm with the majority within 50 ppm. Of the P^{IV} compounds, the phosphate esters

have a very narrow chemical shift range, *ca.* 20 ppm,[75] and to a first approximation it is the substituents attached directly to the P atom which dictate the chemical shift. The ^{31}P chemical shift is rather insensitive to the chemical identity of the groups bonded to the phosphate oxygens,[76] and since the bonding characteristics at phosphorus do not charge significantly, the NMR spectra were therefore not suitable for rate determinations. The ^{31}P signals observed are too close to each other to allow accurate determination of the concentrations of the reactive species and a perusal of the ^{31}P NMR literature containing information regarding phosphate ester chemical shifts supported our findings.

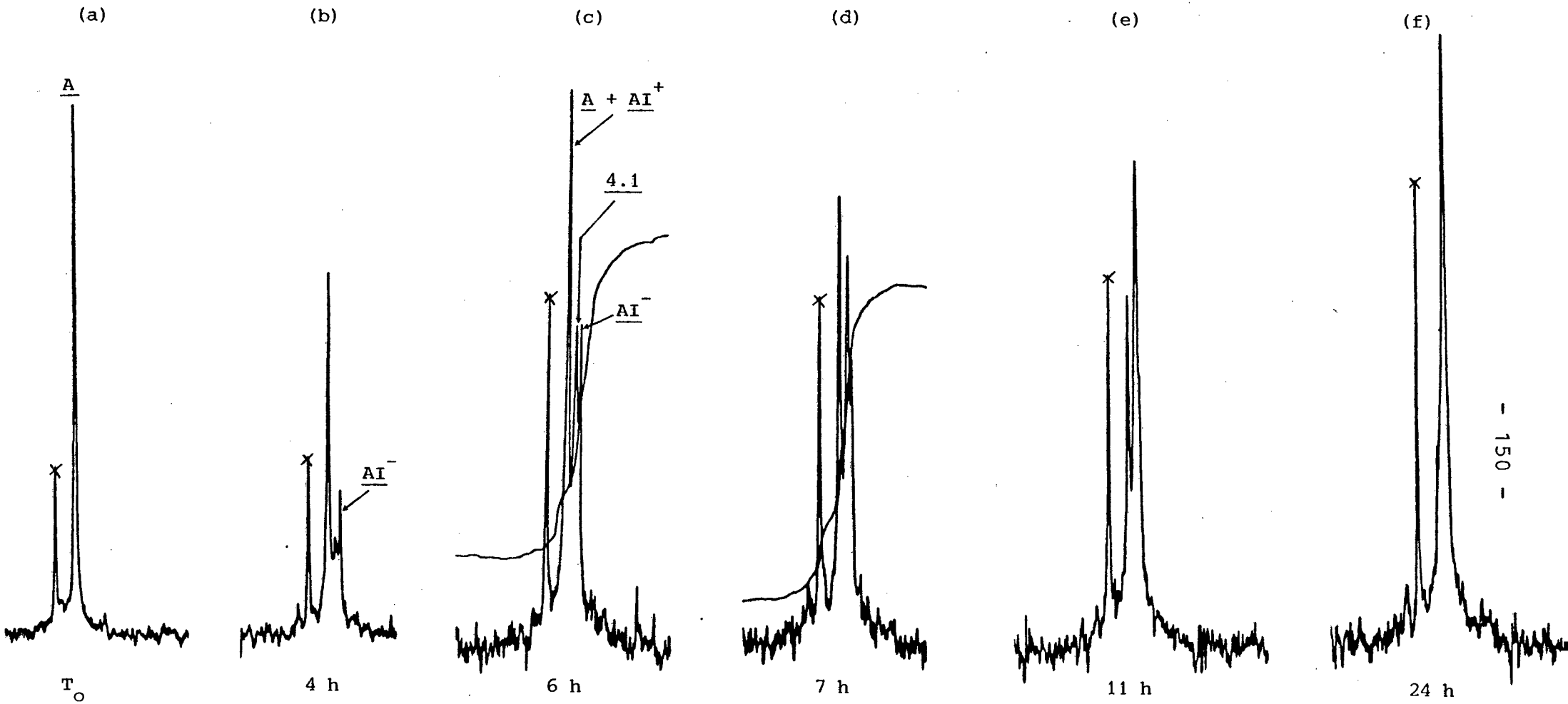


Figure 4.20 A series of ^{31}P NMR spectra which qualitatively illustrate the isomerisation of dimethyl-(2-pyridylmethyl) phosphate in D_2O at 60°C

x = reference (TMP)

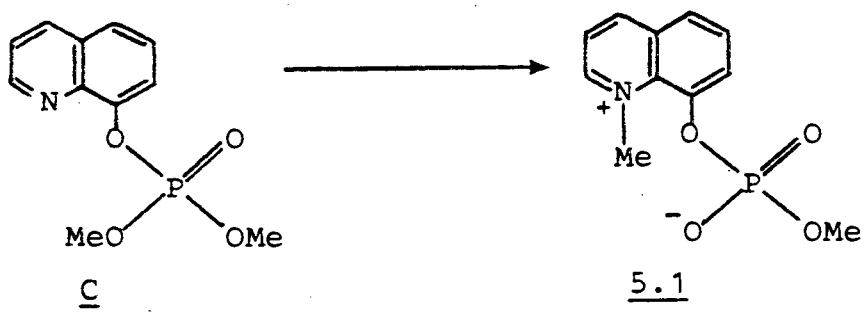
Chapter 5

Reactivity of Dimethyl-(Quinolin-8-yl) Phosphate

5.1 INTRODUCTION

Some years ago, extensive work involving trimethyl phosphate and triethyl phosphate as alkylating agents was reported in the patent literature,[77] and more recently Yamauchi and co-workers reported the use of trialkyl phosphates for the alkylation of N-heterocycles.[78] Later, Frank and Mészáros[79] were involved in further alkylation studies and in particular they investigated the mechanism of the alkylation of 4-quinolone with trimethyl phosphate. These authors found that the dimethyl phosphate salt of quarternary N-methyl-4-methoxyquinolinium catalyses the transformation of 4-methoxy-quinoline by intermolecular O→N methyl transfer to the more stable N-methyl-4-quinolone.

The aim of the present study was to examine O→N methyl transfer during the isomerisation of dimethyl-(quinolin-8-yl) phosphate (eq. 5.1) and as it will shortly be realized this investigation encompasses various avenues of research.



C 5.1 (5.1)

Aside from the possibility of dimethyl-(quinolin-8-yl) phosphate undergoing a bimolecular O→N methyl transfer, its formulation as a reaction system having the potential also for an intramolecular O→N methyl transfer is not unfounded as intramolecular nucleophilic attack at the phosphorus centre by the quinolyl nitrogen has been

reported in the hydrolysis of 4-nitrophenyl-(quinolin-8-yl) phosphate.[14] Although strain in the 5-membered ring formed by the bridging of the 1- and 8-positions of the quinoline nucleus is proposed as the explanation for the less efficient action of this molecule compared to the carboxylate attack in the hydrolysis of 2-carboxyphenyl 4-nitrophenyl phosphate, the strain is insufficient to change the mechanism of the reaction from intramolecular nucleophilic catalysis to general base catalysis. However, we believe that intramolecular nucleophilic attack by the quinolyl nitrogen at the electrophilic phosphorus centre will be unfavourable, not only because the OCH_3 substituent is considered as a 'middle rank nucleofuge'[65] but also because of the preference of a soft nucleophile (the 3° nitrogen)[80] for a soft electrophilic centre (the methyl carbon atom).[81] Aside from a statistical point of view, $N \rightarrow CH_3$ interaction would also be more likely than $N \rightarrow P$ interaction because of the larger ring which would form in the transition state in the former case.

It may be logical to propose that as no intramolecular methyl transfer was observed in the isomerisation of dimethyl-(2-pyridylmethyl) phosphate, then no intramolecular $O \rightarrow N$ methyl transfer is expected in the isomerisation of dimethyl-(quinolin-8-yl) phosphate (a 7-membered cyclic transition state would be involved in both cases). However, it could be argued that intramolecular $N \rightarrow CH_3$ interaction should be more favourable in the 2,3-benzo substituted pyridine than in the 2-methyl substituted pyridine because of the greater rigidity of the POCCN skeleton in the first case. It can also be argued therefore, that this rigidity in the molecular backbone should enhance $N \rightarrow P$ interaction involving a more stable 5-membered

ring in the 8-quinolyl derivative, but we believe for reasons discussed above, that the probability of such an interaction is small.

So, as well as being a bifunctional molecule (nucleophile and electrophile), dimethyl-(quinolin-8-yl) phosphate is also a bifunctional electrophile which may react with nucleophiles both at the phosphorus atom and at the methyl carbon atom. Attack of nucleophiles may therefore lead to P-O or C-O bond cleavage and particular attention is given to this distinction throughout this chapter.

5.2 A SEMI-QUANTITATIVE STUDY OF THE CHEMICAL REACTIVITY OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE

The stability of dimethyl-(quinolin-8-yl) phosphate in deuterated acetone and acetonitrile (0.7 M) was demonstrated by refluxing the substrate for 18 h in these solvents and observing that the ^1H NMR spectrum of the reaction mixture after this time was unchanged. As with the 2-pyridylmethyl and 2-pyridylethyl analogues, a dramatic solvent effect was observed. When a 0.67 M solution of dimethyl-(quinolin-8-yl) phosphate (fig. 5.1a) was refluxed for 2 h in D_2O, the ^1H NMR spectrum of the product mixture (fig. 5.1b) showed no substrate remaining, an intense singlet at δ3.53, a sharp singlet at δ4.82 and traces of two doublets at δ3.77 and δ3.93. Addition of methanol to this mixture confirmed that the singlet at δ3.53 was due to the CH_3 absorption of methanol.

In order to follow the reaction more closely, we prepared a solution of the substrate in D_2O (0.82 M) in an NMR tube and followed the reaction at 60°C by periodically withdrawing the tube from the

water bath, arresting the reaction by immersing the tube in an ice/salt bath and recording the ^{1}H NMR spectrum. Fig. 5.1c shows that after 14 h at 60°C there are three singlets in the $\overset{+}{N}$-CH_3 absorption chemical shift range (δ4.98, 4.93 and 4.82). The singlet at δ4.98 has a transient existence as the subsequent spectra revealed. Fig. 5.1c also illustrates the complexity of the isomerisation reaction. There are apparently four O-methyl doublets within a 0.55 ppm chemical shift range. After 14 days, the NMR spectrum had simplified (fig. 5.1d). Only two N-methyl absorptions remained (in *ca.* 5:1 ratio), there was no unreacted substrate (i.e. no doublet at δ4.22), only two O-methyl doublets were present and a singlet at δ3.53 for methanol was observed. At this stage of the experiment, the contents of the NMR tube were divided into two parts. Addition of authentic dimethyl phosphate (the mono-sodium salt) to one part confirmed the identity of the most high-field (δ3.77) O-methyl doublet. The second half of the reaction mixture was kept in the waterbath at 60°C for another 28 days in order to arrive at the final constant composition of the reaction mixture. Intergration measurements showed that after 12 days, the ratio of the N-methyl absorptions at δ4.93 and δ4.82 had reached a constant value (*ca.* 5:1).* One of the N-methylated products ($\overset{+}{N}$-Me signal at

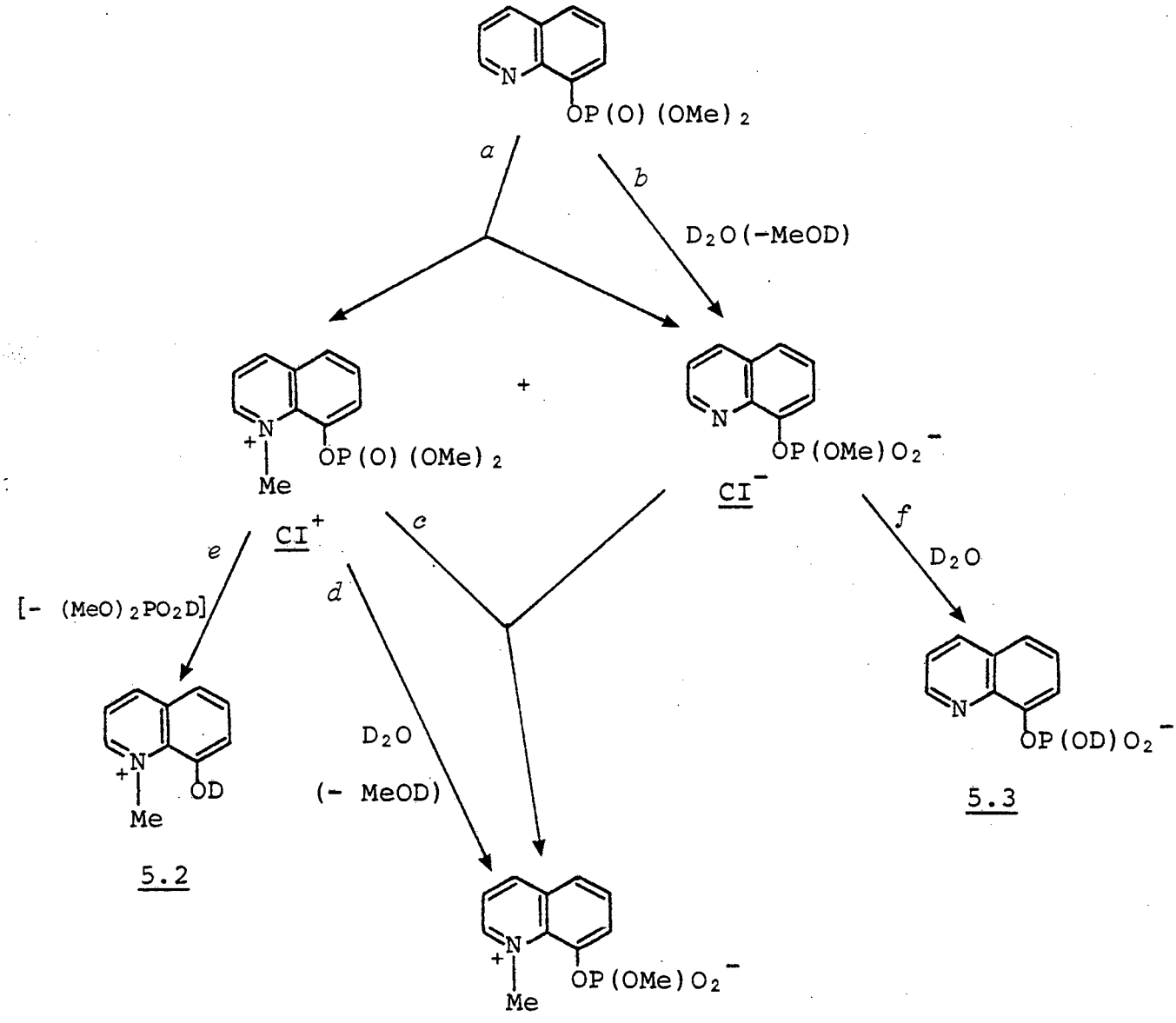
*One problem with this sample was that the HOD solvent absorption (×) masked the major N-methyl absorption when the NMR tube reached the probe temperature (*ca.* 31°c). By keeping the NMR tube in an ice/salt bath prior to recording the spectrum, we were in most cases able to observe both N-methyl signals.

δ4.82) was identified as the N-methyl 8-hydroxyquinolinium ion by addition of an authentic sample of the independently prepared salt.*

Scheme 5.1 illustrates the complexity of the reaction in an aqueous medium. Pathway *a* illustrates the first step of the bimolecular isomerisation reaction leading initially to a pair of ionic intermediates $\underline{CI}^-$ and $\underline{CI}^+$, which then react together (pathway *c*) to form the zwitterionic product (5.1). Scheme 5.1 also shows that the isomerisation of dimethyl-(quinolin-8-yl) phosphate in water is complicated by hydrolysis. Pathway *b* illustrates the nucleophilic attack of water at the methyl carbon atom of the ester function of the substrate which results in the production of methanol and the anionic intermediate $\underline{CI}^-$. Pathway *d* and *e* illustrate the hydrolysis of the intermediate $\underline{CI}^+$ via the attack at carbon and phosphorus respectively. These secondary reactions are discussed in ch. 5.3.2a and ch. 5.3.2b.

*A sample of N-methylated 8-hydroxyquinoline was not isolated in pure form for this purpose, but it was prepared on a small scale in an NMR tube from a stoichiometric mixture of 8-hydroxyquinoline and TMP in a $D_2O/(CD_3)_2CO$ solution (1:2) at 90°C. The remainder of TMP hydrolysed to dimethyl phosphate and methanol. The solvents and methanol were evaporated *in vacuo* leaving the N-methylated 8-hydroxyquinolinium dimethyl phosphate and the excess of 8-hydroxyquinoline.

Scheme 5.1


OP(O)(OMe)2
a
b
D2O(-MeOD)
OP(O)(OMe)2
Me
CI+
OP(OMe)O2-
CI-
e
[- (MeO)2PO2D]
c
d
f
D2O
OD
Me
5.2
D2O
(- MeOD)
OP(OD)O2-
5.3
OP(OMe)O2-
Me
5.1

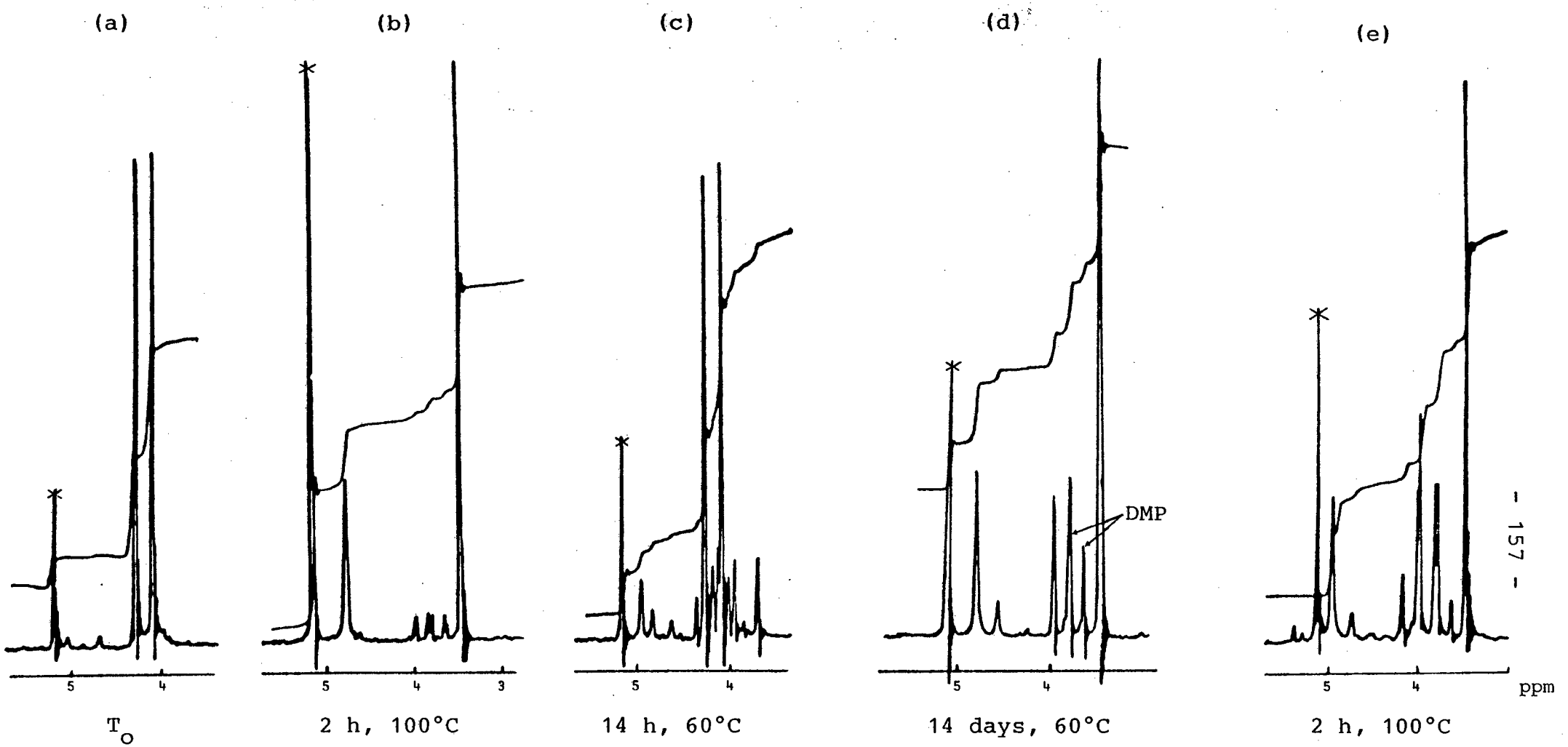


Figure 5.1 Changes in the ^1H NMR spectrum of dimethyl-(quinolin-8-yl) phosphate in D_2O

The results obtained in the previous experiment are only considered as approximate as no special precautions were undertaken to quantitatively determine the amount of methanol formed. Nevertheless, the results from both experiments reveal the potential of compound C to undergo a large number of reactions in these conditions.

When repeating the two experiments, minor adjustments were made. Firstly, instead of placing the D_2O solution directly in a flask which could then be heated, the solution of the substrate (0.67 M) was prepared and placed in an NMR tube. After recording the spectrum the sealed NMR tube was placed in a boiling water bath and the ^1H NMR spectrum recorded periodically. Secondly, the concentration of the sample to be heated at 60°C was increased (to 1.6 M) so as to avoid the problem of the solvent peak hindering the N-methyl absorption and this tube was also sealed. The results obtained from heating the sample in D_2O at 100°C and at 60°C are qualitatively the same, differing only in the rate of reaction. The ^1H NMR spectrum recorded after carrying out the reaction for 2 h at 100°C is given in fig. 5.1e. This spectrum contrasts markedly with fig. 5.1b. It is evident that in the first case, conditions must have been more drastic (higher temperature) and this led to the total disappearance of substrate and to the advanced removal of the methyl groups from the phosphate ester functions. In fig. 5.1e there are three O-methyl doublets, the most low-field corresponding to unreacted substrate. Once again the methanol singlet is very intense. The results obtained from the experiment at 60°C are more informative than the results at 100°C, so these are referred to in the following discussion. A series of NMR spectra showing changes

in the chemical shift range δ3.0 - 6.0 at different times is given in fig. 5.2.

All peak assignments were supported by addition of authentic materials, the synthesis of which are reported in ch. 5.3. Fig. 5.2a shows that after 16 h at 60°C, there is only 52% substrate C remaining. In addition to the substrate O-methyl doublet (δ4.22) there are O-methyl doublets at δ4.33 for the intermediate cationic species CI^+, at δ3.75 for the intermediate anionic species CI^-, at δ3.85 for the zwitterionic product 5.1 and at δ3.77 for dimethyl phosphate. The three singlets at δ4.93, δ4.98 and δ4.82 correspond to the zwitterionic product (5.1), the cationic species (CI^+) and to N-methylated 8-hydroxyquinoline (5.2) respectively. The singlet at δ3.77 for methanol corresponds to *ca.* 5% of the reaction mixture. Figure 5.2b corresponds to heating for 60 h at 60°C. There are four O-methyl doublets which correspond to the substrate (*ca.* 18%), the zwitterionic product, the anionic intermediate and dimethyl phosphate. Consistent with these species are only two N-methyl absorptions - for the zwitterionic product and N-methylated 8-hydroxyquinoline. There is no positively charged intermediate species (CI^+) present. The spectrum recorded after 258 h (fig. 5.2c) is simpler still as there is no unreacted substrate. Finally, after 600 h the reaction mixture consists of methanol, the zwitterionic product (5.1), N-methylated 8-hydroxyquinoline (5.2) and dimethyl phosphate (fig. 5.2d).

We believe that the reaction pathways presented in scheme 5.1 describe the chemical transformations which occur when dimethyl-(quinolin-8-yl) phosphate is heated in water. Support for the

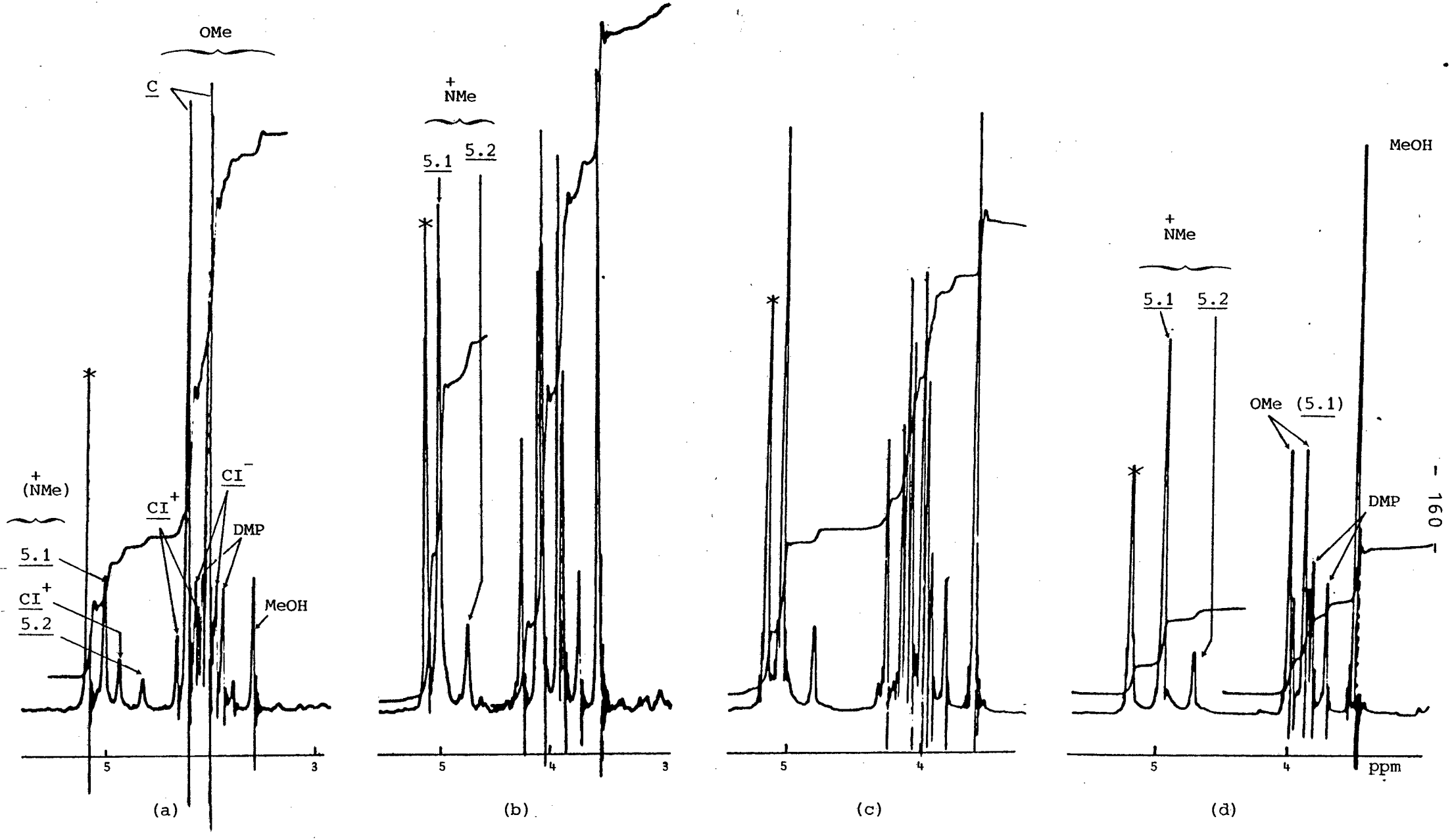


Figure 5.2 Changes in the ^1H NMR spectra of dimethyl-(quinolin-8-yl) phosphate (D_2O, 60°C)

independent pathways was gained by investigating the stability of the individual reactant species under similar conditions. The sodium salt of dimethyl phosphate was unchanged after heating at 60°C for 35 days. However, both the zwitterion (5.1) and the anionic intermediate species $\underline{CI}^-$ were no so resistant to hydrolysis and produced methanol after 30 days at 60°C. Surprising as this result may seem, it is consistent with the NMR spectral data obtained in the above experiment. The reactivity of the cationic intermediate species $\underline{CI}^+$ is described in part 5.4.2 of this chapter. Briefly though, its 'short lived' existence is apparent by its absence from fig. 5.2b-d. It is interesting that the intensity of the doublet corresponding to $\underline{CI}^+$ is always notably less intense than that for the anionic intermediate $\underline{CI}^-$. This means that there are additional reaction pathways available for $\underline{CI}^+$. We believe that $\underline{CI}^+$ is the most reactive of all species shown in scheme 5.1. Also very obvious from the NMR spectra is the absorption due to methanol which almost dominates towards the end of the reaction. Nucleophilic attack of D_2O at the electrophilic carbon methyl ester group of the substrate C, and intermediate $\underline{CI}^+$, is obviously responsible for this. The methylated intermediate is conceivably a stronger methylating reagent than the substrate molecule because of the positive charge at the quinolyl nitrogen. The introduction of an aromatic substituent directly at the ester oxygen of a dimethyl phosphate derivative enhances the possibility of P-O aromatic bond cleavage because of the electron withdrawing effect of the leaving group. The results show, however, that the P-O aromatic bond cleavage (pathway *e*) is less favourable than the Me-OP bond cleavage. In other words, the attack of water at the methyl carbon, coupled

with the departure of the $(C_9H_6NO)(MeO)PO_2^-$ group is easier than the attack at phosphorus, accompanied by the departure of the conjugate base of N-methylated 8-hydroxyquinoline. Using the same argument we suggest that the N-methylated 8-hydroxyquinolinium ion is a final reaction product, rather as a result of P-O aromatic bond cleavage in $\underline{CI}^+$ than in the substrate C.

As shown in scheme 5.1, the reactivity of dimethyl-(quinolin-8-yl) phosphate in water is complicated by hydrolysis reactions. As a result, the reacting system involves two concurrent processes (pathways *a* and *b*), followed by a number of consecutive reactions (pathways *c*, *d*, *e* and eventually *f*). Individual reactions are either second-order (pathways *a* and *c*) or first-order (pathways *b*, *d*, *e* and *f*) with respect to the organic species. The kinetics of a system of this type are virtually insoluble, and we did not attempt to determine rate constants either for the O→N methyl transfer reaction, or for the two competing primary reactions (pathways *a* and *b*). We have, however, prepared a diagram (fig. 5.3) on which is plotted the relative concentrations of individual species observed as a function of the reaction time. This enables us to obtain qualitative support for scheme 5.1 and in addition, it is possible to evaluate the relative importance of the individual pathways.

Figure 5.3 shows that the concentration of the intermediate species $\underline{CI}^+$ reaches a maximum, and decreases rather rapidly to zero, as required by pathways *c*, *d* and *e*. On the other hand, the significant increase in the concentration of $\underline{CI}^-$, well after the disappearance of $\underline{CI}^+$, provides support for the importance of pathway *b*. As for the zwitterionic product (5.1), it cannot appear until a certain

quantity of $\underline{CI}^+$ and $\underline{CI}^-$ have formed. The major product observed in the final NMR spectrum is methanol. If only pathways *b* and *d* were responsible for the production of methanol, then the avenue marked M in fig. 5.3 corresponding to methanol should parallel the curves for the products of these two pathways (5.1 and $\underline{CI}^-$, respectively). However, after 60 h the percentage of $\underline{CI}^-$ begins to decrease despite the continuous increase in the methanol concentration; we ascribe this result to the contribution from pathway *f*. Since the percentage of the zwitterion 5.1 begins to decrease (again at the expense of methanol) only after 542 h at 60°C, we feel justified in considering it as a final reaction product in scheme 5.1. Figure 5.3 also confirms our earlier proposal that the N-methylated 8-hydroxyquinolinium ion (5.2) results from P-O(quinolyl) bond cleavage in $\underline{CI}^+$ rather than in the substrate. At no time does the percentage of dimethyl phosphate in the reaction mixture exceed the percentage of 5.2; in fact the two curves representing the concentration changes of these two species (5.2 and DMP) are practically superimposable.

No intramolecular O → N methyl transfer has been represented in scheme 5.1. The identification of the intermediate species $\underline{CI}^+$ and $\underline{CI}^-$ during the isomerisation reaction provides direct evidence for the bimolecular reaction. Since the complexity of the system made a kinetic analysis impossible, some contribution from the intramolecular pathway to the formation of the zwitterion 5.1 cannot be excluded. In ch. 6 we use information obtained from the crystal structure analysis of dimethyl-(quinolin-8-yl) phosphate to predict the feasibility of intramolecular isomerisation.

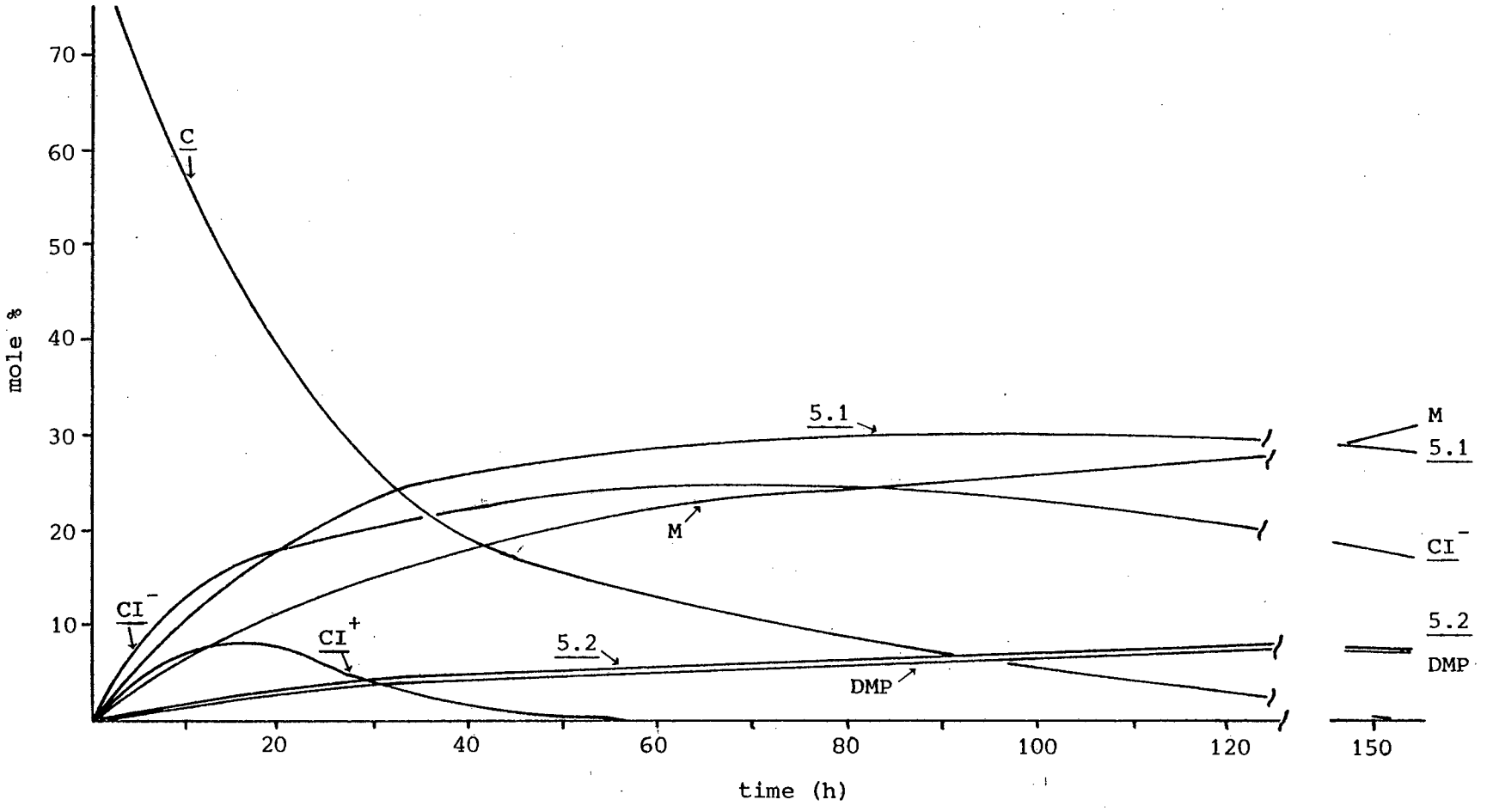


Figure 5.3 Mole % of individual species observed (^{1}H NMR spectroscopy) as a function of time when dimethyl-(quinolin-8-yl) phosphate is heated in D_2O at 60°C

CI⁺,	cationic intermediate	5.2,	N-methylated 8-hydroxyquinoline
CI⁻,	anionic intermediate	DMP,	Dimethyl phosphate
5.1,	zwitterionic product	M,	Methanol

5.3 THE SYNTHESIS OF COMPOUNDS INVOLVED IN SCHEME 5.1.

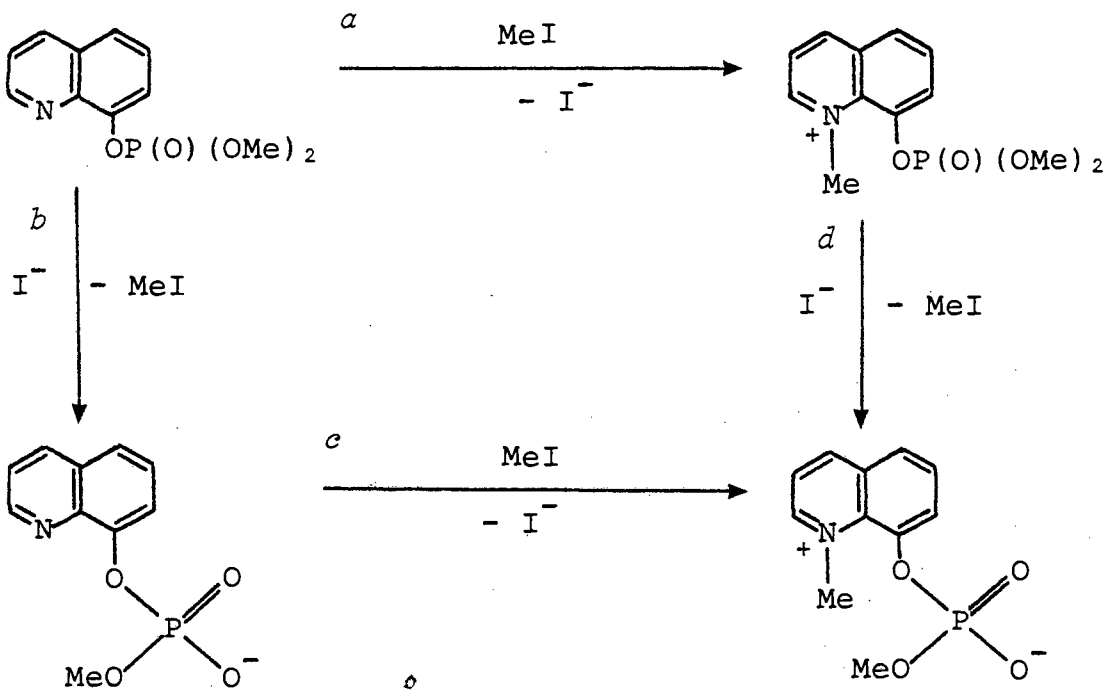
5.3.1 METHYL-[8-(N-METHYLQUINOLINIUM)] PHOSPHATE, 5.1

In ch. 4.1.3, we described the extraction of the zwitterionic product 4.1 from the isomerisation mixture of compound A in D_2O. Isolation of 4.1 was possible because the final reaction mixture was not contaminated with too many side reaction products. However, as scheme 5.1 shows, the isomerisation of dimethyl-(quinolin-8-yl) phosphate in water is fraught with side reactions and this makes the isolation of the zwitterionic product 5.1 from the final reaction mixture a cumbersome task. The primary reaction product - the zwitterion, and the secondary products shown in scheme 5.1 are a direct result of the use of water as the reaction medium. The aqueous medium, however, is a necessary condition for the reaction, and as we discussed in ch. 5.2, dimethyl-(quinolin-8-yl) phosphate does not isomerise in aprotic solvents.

With the use of a hydrogen-bonding solvent an additional nucleophile (water) is introduced into the reaction system. We have already seen that in the isomerisation of dimethyl-(2-pyridylmethyl) phosphate, participation by water as a nucleophile was minimal. However, it is the nature of the ester groups at phosphorus which determine the degree of interference by water. With one aromatic ester substituent at phosphorus, the reaction of water at phosphorus and/or carbon is more favourable because of the good leaving ability of an aromatic group. Hence the reaction becomes more complicated. We therefore decided to carry out the isomerisation of C in an aprotic inert medium and to promote the reaction by addition of iodomethane. In this capacity, iodomethane was expected not only to serve as the initial methylating agent, but also as a precursor

of iodide ion, which in turn would perform the function of a demethylation agent (scheme 5.2).

Scheme 5.2



In the first instance, iodomethane quarternizes nitrogen (pathway *a*) to form N-methylated dimethyl-(quinolin-8-yl) phosphate. The iodide ion which is generated can then demethylate this product (pathway *d*) to form the zwitterion or it can demethylate the substrate (pathway *b*) to form the O-demethylated substrate and iodomethane. The iodomethane generated or the authentic iodomethane, introduced as the substrate at the beginning of the reaction sequence, can then methylate nitrogen (pathway *c*) to form the zwitterionic product.

Since the major objective in synthesizing the zwitterionic product was to obtain a pure sample for characterization and identification purposes, we did not attempt to investigate the mechanism of the

reactions shown in scheme 5.2, i.e. to determine the rate constants and relative contribution of individual methylation and demethylation steps. Such an investigation would require using carbon-labelled iodomethane and measuring the effect of the initial iodomethane concentration on the rate of the reaction. To obtain some preliminary information regarding the optimum conditions for the preparation of the zwitterion, we carried out the isomerisation of the triester in deuterated acetone using 1 (experiment A) and 0.1 (experiment B) mole-equivalents of iodomethane. Both reactions were carried out in sealed NMR tubes placed in a water bath at 60°C. In experiment A, after 12 days the tube was full of needle-shaped crystals and the ^{1}H NMR spectrum showed that the solution contained only iodomethane; its quantity, as measured relative to TMS remained unchanged. The crystalline product was then identified as the required product by means of its ^{1}H NMR (D_2O) spectrum: δ 3.85 (3H, d, $J_{H,P}$ 11Hz, POMe); 4.93 (3H, s, $\overset{+}{N}$-Me), and 7.93 - 9.37 (5H, showing the usual pattern for 8-substituted quinolinium systems). The structure of this compound was additionally confirmed by elemental analysis.

Much poorer results were obtained from experiment B: a dark oily product separated and the ^{1}H NMR spectrum of the final mixture revealed that the reaction was incomplete (e.g. two $\overset{+}{N}$-Me signals, δ4.82 and 4.97 were observed). These results show that the conditions applied in experiment A represent an excellent method for the quantitative isomerisation of the triester into its zwitterionic form. The inferior results obtained from experiment B indicate that the isomerisation proceeds most probably *via* pathways *a*, *d* (scheme 5.2), step *a* (N-methylation) being rate-determining in the overall process.

5.3.2a DIMETHYL-[8-(N-METHYLQUINOLINIUM)] PHOSPHATE TRIFLUOROMETHANESULFONATE, CI$^+$

Trifluoromethanesulfonate esters are probably the most powerful alkylating agents of their type[82] which is hardly surprising since trifluoromethanesulfonic acid is an extremely strong acid[83] and its anion should be an excellent leaving group. N-alkylation readily occurs with these esters and even N-alkylation of the sterically hindered base 2,6-lutidine has been effected rapidly at room temperature.[84]

Initially the methylation of dimethyl-(quinolin-8-yl) phosphate was attempted by dissolving the phosphate triester in a minimum volume of chloroform and adding a stoichiometric equivalent of methyl trifluoromethanesulfonate. This addition was accompanied by a strong exothermic effect. The mixture was stirred at room temperature for 1 h. Addition of ether resulted in an oil separating out of solution. The solvents were removed *in vacuo* and the ^{1}H NMR (D_2O) spectrum of the viscous oil revealed that N-alkylation had occurred essentially quantitatively. The identity of the compound was confirmed by its NMR spectral characteristics. A singlet at δ4.98 intergrating for three protons is assigned to the N-methyl absorption and the symmetrical doublet for the P-OCH$_3$ protons has shifted downfield to δ4.33 from δ4.22 in the starting material. Attempts to crystallize the product proved very difficult. Precipitation from acetonitrile was effected but the ^{1}H NMR (D_2O) spectrum of the solid powdery material disclosed that the product was unstable and had formed dimethyl phosphate and the N-methylated salt of 8-hydroxyquinoline. Elemental analysis also

confirmed that the yellow powder-like solid was not the desired product.

Since methyl trifluoromethanesulfonate is sparingly soluble in chloroform, methylation was repeated using nitromethane as a solvent. A clear solution was obtained, which after addition of ether and cooling, deposited an oily product. Removal of the solvents under reduced pressure gave a viscous orange-coloured oil (84%). The product was identified by its ^{1}H NMR spectrum, which was identical to that obtained in the previous experiment. No attempts to obtain this product in a crystalline state were made, but its purity was confirmed by elemental analysis.

The plethora of literature published on the use of esters of trifluoromethanesulfonic acid as alkylating agents[82] demonstrates the exceptional strength of these reagents. However, in spite of all these reports, with the exception of a publication by Mikolajczyk and Omelańczuk[85] for the stereospecific synthesis of a chiral 3° phosphinite, there is little literature evidence for methylation at the phosphoryl oxygen during reactions utilizing methyl trifluoromethanesulfonate. We believe that the mild conditions and the stoichiometric substrate to alkylating reagent ratio used, ensured that the alkylation occurred only at the quinolyl nitrogen.

Since we observed that the target compound decomposed easily (yielding dimethyl phosphate and N-methylated 8-hydroxyquinolinium ion) during the work-up, we decided to check the stability of this product in the aqueous medium. Figures 5.4b-d show changes in the ^{1}H NMR spectrum of the product in D_2O at room temperature over 26 days.

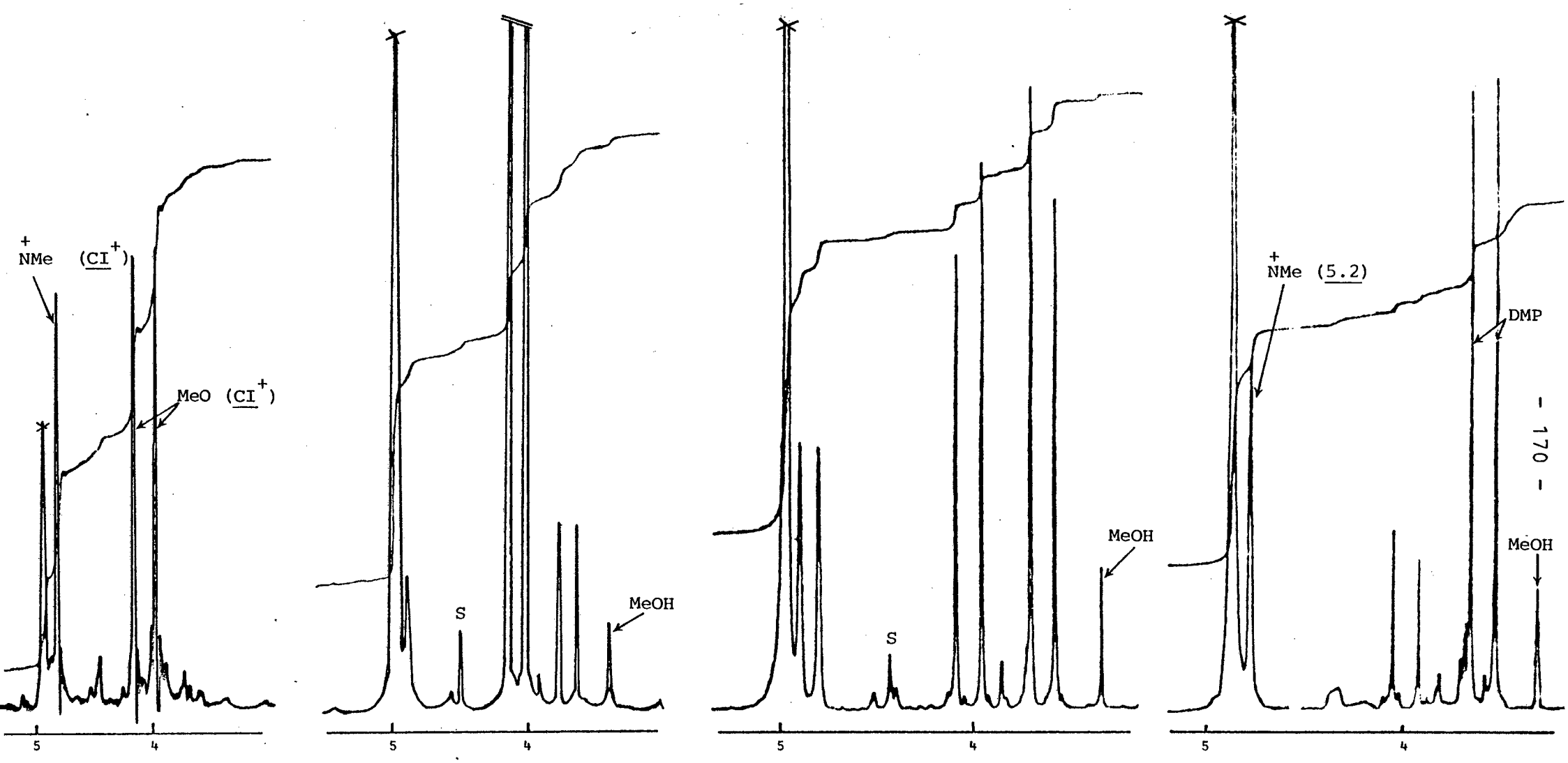
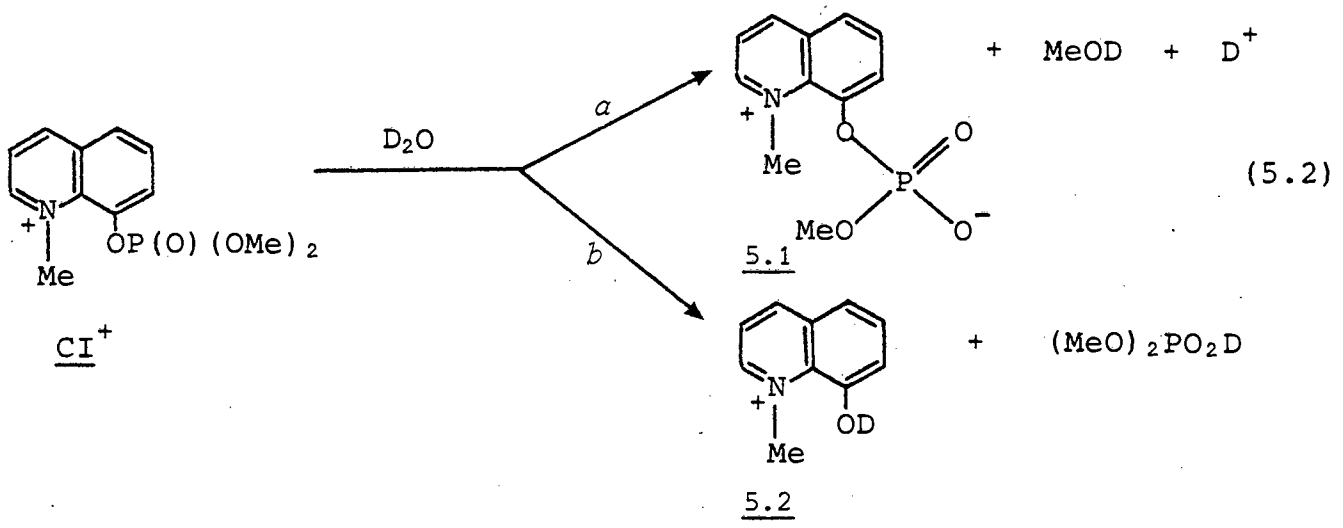


Figure 5.4 Changes in the ^1H NMR spectra of $\underline{CI}^+$ in D_2O at 22°C.

(S is solvent peak, CH_3NO_2).

There are two electrophilic centres in CI$^+$ and consequently there are two reaction pathways available for nucleophilic attack, *viz.*, attack of water (D_2O) at methyl carbon to form methanol and methyl-[8-(N-methylquinolinium)] phosphate (pathway *a* eq. 5.2), or attack at phosphorus with P-O-quinolyl bond cleavage forming dimethyl phosphate and a N-methylated 8-hydroxyquinolinium derivative (pathway *b* eq. 5.2).



(5.2)

Figure 5.4d clearly demonstrates that virtually only pathway *b* is operable under the circumstances. The singlet at δ3.53 due to methanol does not increase in intensity from fig. 5.4a through to 5.4d and its presence is more than likely due to some unreacted methyl trifluoromethanesulfonate present at T_o which hydrolyses to methanol. The hydrolysis of methyl trifluoromethanesulfonate has recently been described as too rapid at room temperature to be followed by conventional techniques.[86] The identity of the species present in the final reaction mixture was confirmed by addition of the following authentic materials: 8-hydroxy-(N-methylquinolinium) iodide which confirmed the identity of the N-methyl absorption at δ4.82 (the preparation of this compound is discussed in part 5.3.4 of this chapter); sodium dimethyl phosphate which was prepared by

the method described by McIvor *et al.*[87] using trimethyl phosphate and sodium hydroxide; and methanol.

In order to investigate the hydrolytic reactivity of the $\underline{CI}^+$ ion more closely, we decided to prepare this salt with a different counterion, which would hopefully enable us to isolate the product in a crystalline form. Dimethyl sulphate was chosen as the methylating agent.

5.3.2b DIMETHYL-[8-(N-METHYLQUINOLINIUM)] PHOSPHATE METHYLSULPHATE, $\underline{CI}^+$

The methylation was accomplished by adding dimethyl-(quinolin-8-yl) phosphate to a ten-fold excess of dimethyl sulphate, at room temperature and with stirring. After the substrate had dissolved, the mixture was heated at 100°C in an oil bath for 2.5 h and then stirred overnight at room temperature. The reaction mixture was protected at all times from moisture. The almost pure product was obtained after washing the mixture with diethyl ether. However, the analytically pure compound could not be obtained because of the difficulty again encountered in removing the residual amounts of alkylating agent. The ^{1}H NMR (D_2O) spectrum was essentially identical to that obtained using methyl trifluoromethanesulfonate as the alkylating agent - the one noticeable difference being the singlet at δ3.76 for the methylsulphate anionic group which intergrated for three protons. The decomposition of the methylsulphate salt in water (see eq. 5.2) was investigated by ^{1}H NMR spectroscopy at three different temperatures and the results, expressed in terms of the ratio of nucleophilic attack at methyl carbon versus

phosphorus, *viz.*, C/P, are shown in table 5.1. The C/Pst value represents the statistically corrected ratio. The values quoted are the average of at least two experiments at each temperature. The results reveal that nucleophilic attack of water at carbon is on average 1.85 x more favourable than attack at phosphorus.

Table 5.1 Selectivity in the hydrolysis of $\underline{CI}^+$

	25°C	45°C	60°C	Average value
C/P	3.53	3.56	4.01	3.7
C/Pst	1.77	1.78	2.01	1.85

A ^{1}H NMR spectrum typical for a final result is shown in fig. 5.6. Characterization of the ^{1}H NMR signals was supported by the addition of the authentic materials: methyl-[8-(N-methylquinolinium)] phosphate; sodium dimethyl phosphate; 8-hydroxy-(N-methylquinolinium) iodide and methanol.

The selectivity in hydrolysis observed for the methylsulphate salt differs greatly from that obtained for the trifluoromethanesulfonate derivative. We believe that in the latter case, the hydrolysis is catalysed[88] by some trifluoromethanesulfonic acid present in the reaction medium. Any catalytic effect due to the participation of fluoride ions[89] seems unlikely in view of the reported[82] stability of trifluoromethanesulfonic acid and its anion.

Our results show that mixed aryl/alkyl phosphate triesters are versatile compounds under hydrolysis conditions. Their reactivity

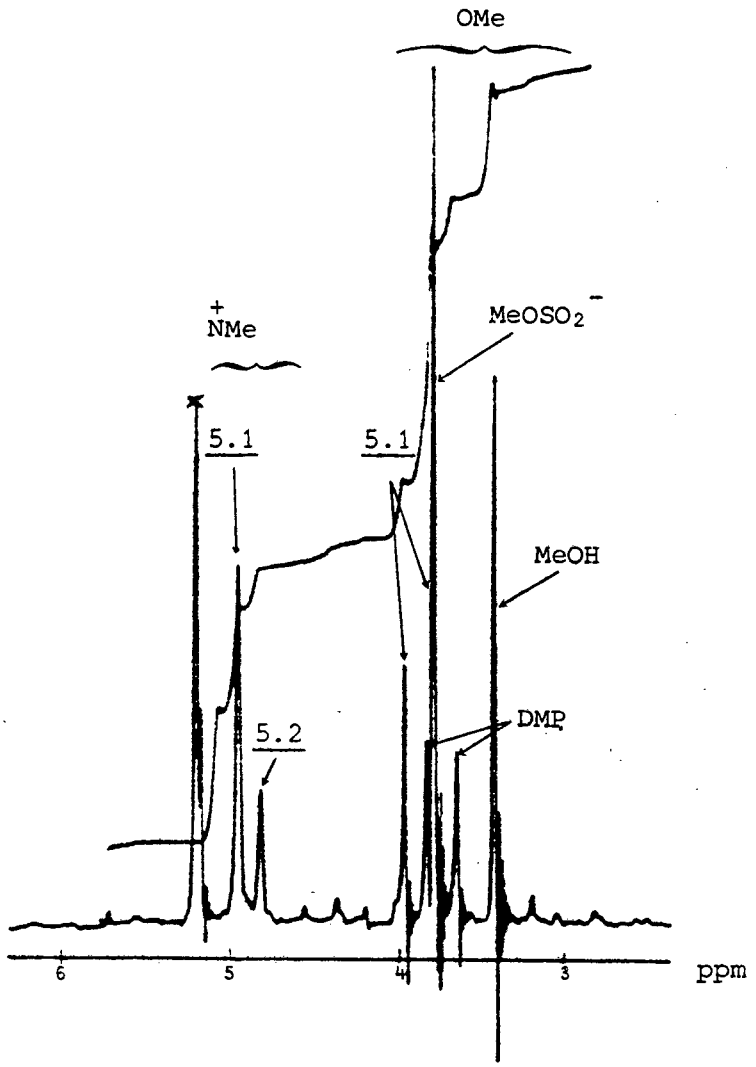


Figure 5.5 ^{1}H NMR spectrum showing final products formed from the reaction of substrate $\underline{CI}^{+}$ in D_2O

depends not only on the pH of the medium but also on the pK_a of the leaving group. In neutral conditions we observed that the hydrolysis of dimethyl-[8-(N-methylquinolinium)] phosphate methylsulphate occurs with predominantly Me-O bond cleavage and to a lesser extent with P-OAr bond cleavage. Although the alkaline hydrolysis of another mixed dialkyl/aryl phosphate triester - dimethyl p-nitrophenyl phosphate, has been reported in the literature to occur with P-O bond cleavage,[90] a direct comparison with dimethyl-[8-(N-methylquinolinium)] phosphate methylsulphate is only possible if the pk_a values of similarly charged leaving groups are known.

5.3.3. THE MONO-SODIUM SALT OF 8-QUINOLYLMETHYL PHOSPHATE, CI$^-$

The demethylation of dimethyl-(8-quinolyl) phosphate was carried out with sodium iodide in refluxing acetone and proved much simpler than the demethylation of the 2-pyridylmethyl analogue, A. No N-methylation of the quinolyl nitrogen nor acetone dimer formation was found to occur. The reaction conditions were identical to those used for the formation of AI$^-$. The reaction is less complicated in the present case because of the introduction of an aromatic carbon atom at the ester oxygen function of the third ester group. This sp^2 hybridised carbon atom imparts stability to this ester group which results in the dealkylation reaction being exclusively selective.

Although a pale yellow precipitate was found to separate out of the reaction solution almost immediately, the mixture was refluxed for 4 h, so ensuring that the reaction was taken to completion. The dealkylated salt was recovered from the acetone solution in

almost pure form by centrifugation. It was extremely hygroscopic. The ^{1}H NMR (D_2O) spectrum confirmed the identity of the salt and the ratio of the intergration for the O-methyl protons:quinolyl protons was now 1:2 as expected. The introduction of a negative charge at one of the ester groups results in the doublet for the O-methyl protons to shift upfield to δ3.75. The salt was dissolved in a minimum volume of dry acetonitrile and then poured into ether. A white precipitate formed immediately and the mono-sodium salt of 8-quinolylmethyl phosphate was collected by centrifugation. The salt was stored in a dessicator over di-phosphorus pentoxide at all times. The elemental analysis corresponded to 1 molecule of water per molecule of product.

5.3.4 8-HYDROXY-(N-METHYLQUINOLINIUM) IODIDE

In order to be able to identify the N-methyl absorption of N-methylated 8-hydroxyquinoline in a reaction mixture, it was necessary to prepare this derivative independently. Iodomethane was the methylating agent of choice as it has been used successfully in numerous quarternization reactions.[91] However, iodomethane has been known to cause O-methylation of phenols and carboxylic acids[92] so cognizance was taken of the possibility of this ether formation.

The salt was prepared by dissolving 8-hydroxyquinoline in a 100-fold excess of iodomethane and leaving the reaction mixture to stand at room temperature. The solution was initially yellow but turned orange after a few hours. Six days later, the first crop

of brown transluscent crystals had appeared. These were collected from the mother liquor by filtration, washed with ether and allowed to dry under vacuum. The ^{1}H NMR spectrum (DMSO-d_6) of the crystals showed a singlet at δ4.95 intergrating, as expected, for half the number of quinolyl protons. This product was recrystallized from propanol/water and elemental analysis revealed that one molecule of water was present for each molecule of salt.

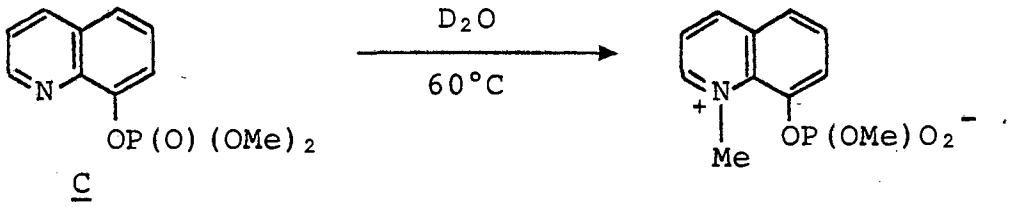
When the reaction was repeated and the mother liquor left to stand at room temperature for ten days, in addition to the brown transluscent crystals, morphologically different crystals (pale yellow and needle-like) were obtained. These latter crystals were well soluble in water so separation of the two types of crystals was easily effected. The ^{1}H NMR spectrum (D_2O) of these crystals revealed both an N-methyl (δ4.92) and an O-methyl (δ3.90) singlet in a 1:1 ratio which confirmed that both N- and O-methylation had occurred.

5.4 A SEMI-QUANTITATIVE STUDY OF O→N METHYL TRANSFER IN QUINOLYL DERIVATIVES

5.4.1 INTRODUCTION

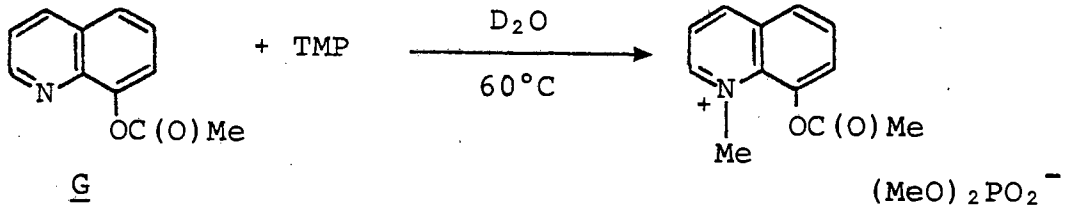
Continuing along the same lines used in ch. 4.1.5 and ch. 4.2.3 where the O→N methyl transfer in dimethylphosphoryloxy (systems I and IV) and acetoxy (systems II and V) derivatives of 2-pyridylmethanol, β-(2-pyridyl)-ethanol, as well as these parent alcohols (systems III and IV), an analogous study in the quinolyl series was attempted, *viz.*, dimethyl-(quinolin-8-yl) phosphate (system VII), 8-quinolyl acetate + TMP (as methylating agent) (system VIII) and 8-hydroxyquinoline + TMP (system IX).

SYSTEM VII



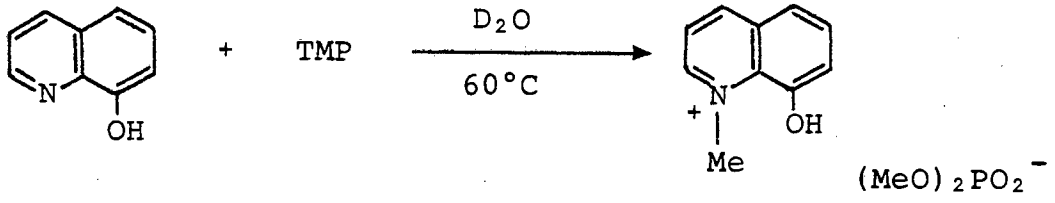
C (5.3)

SYSTEM VIII



G (5.4)

SYSTEM IX



(5.5)

5.4.2 RESULTS AND DISCUSSION

Three major problems were encountered in this investigation. Firstly, the poor solubility of 8-hydroxyquinoline in water excluded pure D_2O as a reaction medium. The reactions were therefore carried out in 20% or 30% (v/v) D_2O in $(CD_3)_2CO$ - this composition being satisfactory from both the solubility and reactivity points of view. Because of the solubility problems, the substrate concentrations were lowered to *ca.* one fourth of those used for previous substrates (systems I - VI). It must be remembered, however, that the results obtained under these conditions cannot be quantitatively compared with the results for systems I - VI, obtained in aqueous media. Secondly, the complexity of the reaction of dimethyl-(quinolin-8-yl) phosphate in aqueous media (see scheme 5.1) made any rate determinations very inaccurate. An approximate second-order rate constant for the rate of disappearance of the substrate C was, however, obtained from the initial section of the plot of the term $x/a_o(a_o-x)$ versus time. Thirdly, an independent experiment involving monitoring the stability of 8-quinolyl acetate in the aqueous acetone mixture by ^1H NMR spectroscopy, revealed that O→N methyl transfer from TMP to 8-quinolyl acetate would be negligible (see later) compared to the hydrolysis of the substrate's ester function. In fact a detailed kinetic study of the hydrolysis of 8-quinolyl acetate[93] has indicated that the enhanced hydrolysis rate was due to an intramolecular nucleophilic catalysis. We were therefore unable to include system VIII in a comparative study with systems VII and IX.

The kinetic results are summarized in table 5.2.

A 10% increase in the volume percentage of water decreases the half-life for the reaction of dimethyl-(quinolin-8-yl) phosphate by approximately 30 h. The results for system IX are less accurate as this reaction was very slow. Besides the solvent effect on the rates of the methyl transfer reaction itself, another interesting observation is the medium effect on selectivity in the reaction of dimethyl-(quinolin-8-yl) phosphate with water. We have seen earlier that attack by water occurs at both the phosphorus centre and at the methyl carbon atoms, and as table 5.3 and fig. 5.6 show, the relative contribution of these two reactions is also dependent on the composition of the solvent. There are two pairs of reaction products: the zwitterion 5.1 and methanol and N-methylated 8-hydroxyquinoline and DMP. The former pair results from attack at methyl carbon and the second pair from attack at the phosphorus atom. The reactions can be expressed as follows.

$$\underline{C} + nH_2O \longrightarrow \cdot \quad \text{reaction at Carbon}$$

$$\text{Rate of reaction at Carbon} = k_c[\underline{C}][H_2O]^n \qquad (5.6)$$

and

$$\underline{C} + mH_2O \longrightarrow \quad \text{reaction at Phosphorus}$$

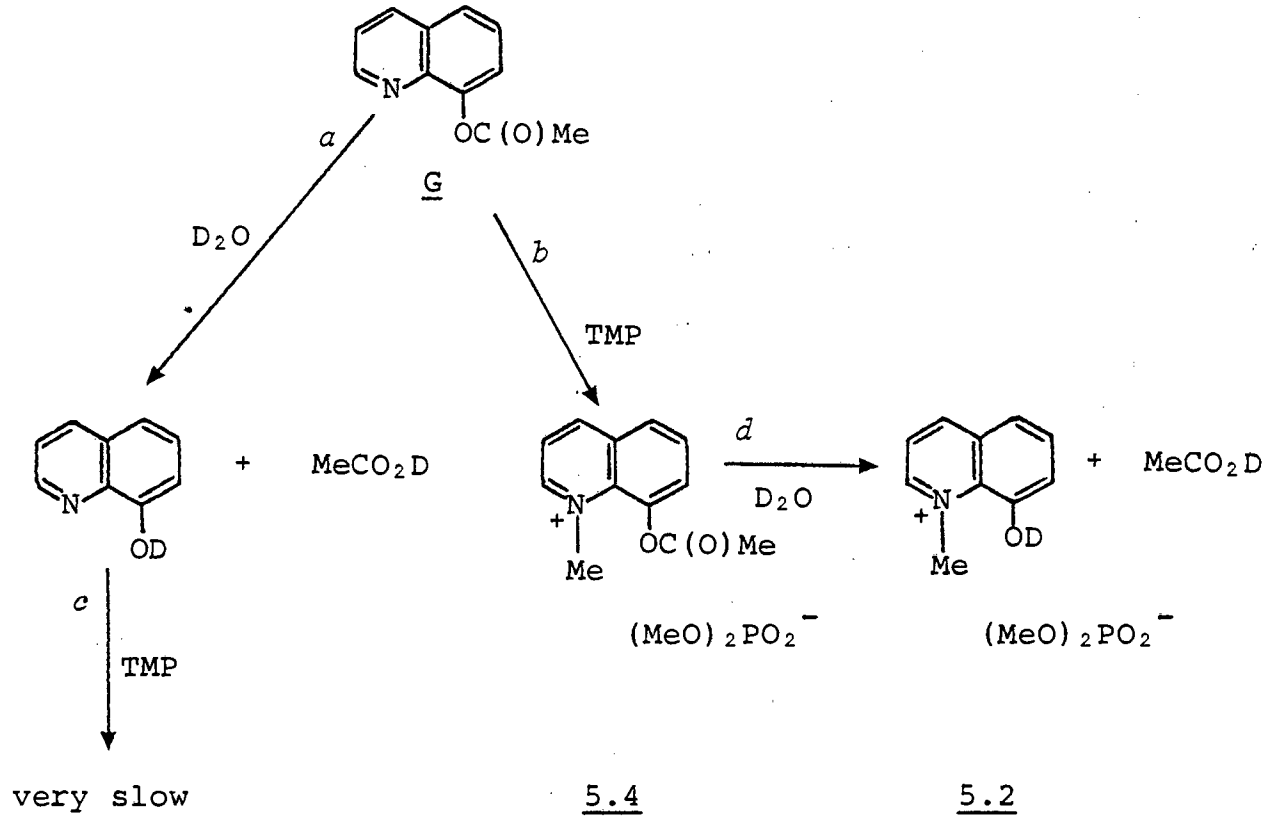
$$\text{Rate of reaction at Phosphorus} = k_p[\underline{C}][H_2O]^m \qquad (5.7)$$

From table 5.3 it can be concluded that $n > m$, i.e. that the attack at methyl carbon (or the transition state of this reaction) has greater hydration requirements than has the nucleophilic attack at phosphorus. This marked difference in the response of the selectivity of hydrolysis to the availability of water in the reaction medium is, in our opinion, another manifestation of the effect of

water (and probably other hydroxylic solvents) on the alkylating properties of alkyl phosphates. Our results indicate that the structural change phosphoric triester → phosphoric diester (attack at carbon) involves greater changes in hydration than does the formation of the P^V intermediates from the phosphoryl substrate.

Scheme 5.3 shows the reactions which are predicted for reaction of 8-quinolyl acetate with TMP in an aqueous medium.

Scheme 5.3



A control experiment designed to calculate the contribution of pathway *a* to the above reaction involved preparing a 0.8 M solution of substrate G in a $D_2O/(CD_3)_2CO$ (20:80 volume %) mixture. The rate of ester hydrolysis was calculated as $9.2 \times 10^{-3} h^{-1}$ ($t_{\frac{1}{2}}$ = 73 h).

An approximate estimate of the contribution of pathway *b* indicates that less than 2.5% of the O→N methyl transfer should take place after 73 h. Since we have found that the reaction represented by pathway *c* is very slow, it is not necessary to make a distinction between products 5.4 and 5.2, as both result from pathway *b*. Consequently, as the contribution of N-methylation of G by TMP is very small relative to the substrate's hydrolysis (the ratio of pathways $a/b > 20$), 8-quinolyl acetate is not a suitable compound for inclusion into the quinolyl series for a comparison of the O→N methyl transfer reaction in aqueous media.

5.4.3 SYNTHESIS OF 8-QUINOLYL ACETATE

Although 8-quinolyl acetate was successfully prepared using zinc chloride as the catalyst, the overall yield was low (53%) and a much more satisfactory result was obtained by using sodium acetate as the catalyst. The synthesis involved heating sodium acetate and 8-hydroxyquinoline in acetic anhydride (used as the acetylating reagent and the solvent) for 2 h at 80°C. The mixture was then poured onto crushed ice and stirred vigorously to effect hydrolysis of acetic anhydride and precipitation of the product. The product was collected by filtration and washed well with iced water to remove acetic acid. It was then dried in a dessicator over P_4O_{10} and sodium hydroxide. The grey powder was characterized by ^1H NMR spectroscopy, mass spectroscopy and elemental analysis.

Table 5.2 Kinetic results of methyl transfer and/or hydrolysis in quinolyl derivatives

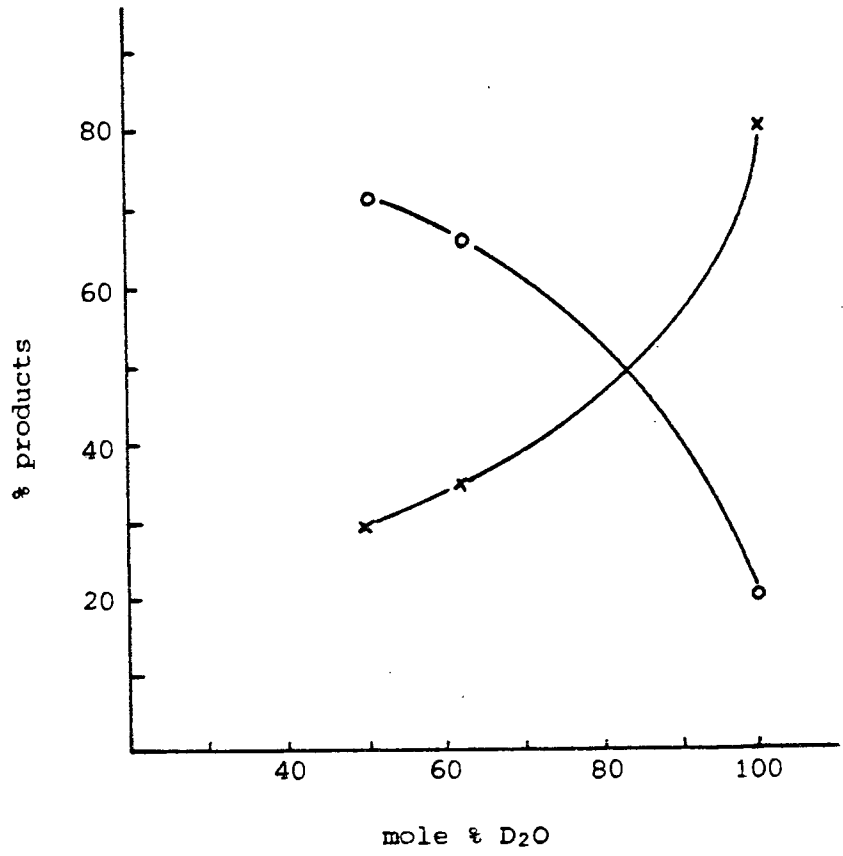
System	Concentration M	Volume % D_2O	10^2k_2 ($M^{-1}h^{-1}$)	10^2k_1 (h^{-1})	$t_{\frac{1}{2}}$ (h)	r
VII	0.8	20	0.7	-	179	0.9973
VII	0.71	30	0.95	-	150	0.9835
C	1.6	100	4.8	-	1.3	0.9953
IX	0.8	20	0.05	-	*ca.* 2270[a]	0.9906
IX	0.71	30	0.06	-	"	0.9937
G	0.8	20	-	0.92	73	0.9952

[a]This value is approximate and it was calculated from the equation $t_{\frac{1}{2}} = t_{1/4}/0.33$

Table 5.3 Medium Effect on Selectivity of Reaction (5.3)

Volume % D_2O	Reaction at C	Reaction at P
100	80	20
30	34	66
20	29	71

Figure 5.6 Plot of % reaction of D_2O at methyl carbon or at phosphorus in substrate C as a function of molar composition of solvent ($D_2O/(CD_3)_2O$) at 60°C.



x reaction at carbon

o reaction at phosphorus

Chapter 6

The Molecular and Crystal Structure of Dimethyl-(Quinolin-8-yl) Phosphate

6.1 INTRODUCTION

A knowledge of the molecular and crystal structure of a compound forms an essential background to the complete understanding of the reactivity and behaviour of that compound. A correlation between the geometrical or solid-state parameters and the properties of dimethyl-(quinolin-8-yl) phosphate in solution is therefore of great interest. In the preceeding chapter, we proposed (on the basis of our kinetic results) that O → N methyl transfer occurs *via* the intermolecular pathway. The rationale for the operation of the bimolecular mechanism as opposed to the intramolecular mechanism can arise from one or two factors. Firstly, no particular steric hindrance would be expected for the nitrogen atom of one molecule of substrate to achieve linear orientation with respect to the CH_3 - O bond of a second molecule (the geometry required by a typical S_N2 process). And secondly, intramolecular nucleophilic attack by the quinolyl nitrogen at the electrophilic methyl carbon ester function may be constrained not to occur because of the deviation from the ideal 180° orientation of nucleophile, methyl carbon, and leaving group in the 7-membered cyclic transition state. If suitable positioning were observed in the solid state structure (i.e. if each nitrogen was in close alignment with a methyl ester group of an adjacent molecule), it would be conceivable that intermolecular nucleophilic attack of the quinolyl nitrogen at the neighbouring methyl group could occur not only in solution but also in the solid state. Recently it was reported[94] that methyl p-(dimethylamino)benzenesulfonate rearranges to p-(trimethylammonium)benzenesulfonate zwitterion about 25 times faster as a solid at 81° than as a melt at 95°.

X-ray data revealed that the nitrogens are almost perfectly aligned with respect to the O-methyl group of an adjacent molecule, so it is the actual nature of the cyrstal lattice which plays an important role in its reactivity and promotes the transformation.

The molecular and crystal structure determination of dimethyl-(quinolin-8-yl) phosphate was therefore undertaken with the following objectives in mind:

1) To compare the results in the previous chapter with crystal structure evidence and to perhaps bridge crystallography with the reaction mechanism.
2) To investigate the potential of the system for an orientation related, solid state methyl transfer reaction.

6.2 EXPERIMENTAL

Dimethyl-(quinolin-8-yl) phosphate was prepared according to the method described in ch. 3.4. The ester was obtained as a low melting (m.p. 69-71°) waxy, pale-yellow solid and failed to produce crystals by the more commonly practiced procedures used for growing crystals. The following methods of growing crystals were attempted:

i) Saturated or nearly saturated solutions of dimethyl-(quinolin-8-yl) phosphate were allowed to stand under conditions where the solvent evaporates slowly. This was carried out using the following solvents: chloroform; acetone; acetonitrile; methanol; dichloromethane; nitromethane; and isopropanol. Only in some cases was a microcrystalline crust deposited on the walls of the sample vessel. In most cases, slow solvent evaporation resulted

in an oil.

ii) Crystallization by solute diffusion, or layering, which depends on the differences in density to maintain the initial separation between two solvents was attempted using the following combinations of solvent (the first named solvent is the solvent in which the substrate is more or only soluble): acetonitrile/carbon tetrachloride; dichloromethane/pet. ether; water/diethyl ether; methanol/pet. ether; nitromethane/carbon tetrachloride; nitromethane/pet. ether; chloroform/carbon tetrachloride; chloroform/pet. ether; chloroform/diethyl ether; benzene/pet. ether; and benzene/carbon tetrachloride. No crystals appeared at the interface between the two solvents as the solvents mixed by diffusion.

The first indication of the ester having crystalline properties was obtained when it was decided to synthesize additional substrate. The synthesis described in ch. 3.4 was now considered to be a routine matter as it had been repeated and yielded pure, but waxy product. In this third attempt to synthesize dimethyl (quinolin-8-yl) phosphate, the product was shown by ^{1}H NMR spectroscopy to contain in addition to the desired ester, some unreacted 8-hydroxyquinoline. Its presence was detected by the unambiguous doublet of doublets. at δ8.87 ($CDCl_3$) which was assigned to the proton *ortho* to the quinolyl nitrogen. This signal shifts 0.18 ppm downfield upon phosphorylation due to the electron withdrawing effect of the phosphoryl group which was transmitted to this *ortho* proton by conjugation. Attempts to remove the starting material included, firstly, a small-scale column chromatographic separation on a

silica gel column. This proved partially successful as it afforded pure dimethyl-(quinolin-8-yl) phosphate (still as a waxy solid, 20%), but unfortunately the product also underwent a significant amount of decomposition and produced even still more 8-hydroxyquinoline, along with dimethyl phosphate. This method was considered very wasteful of the phosphate ester. The second method for purification involved washing the mixture with water. The previous chapter describes the isomerisation of dimethyl-(quinolin-8-yl phosphate to the N-methylated zwitterionic compound - in water, so it was with resignation that we resorted to purification by washing with water. However, the solubility of the substrate and the product is very similar in a wide range of solvents tested and water was found to be one solvent in which 8-hydroxyquinoline was poorly soluble, yet in which the product was well soluble. A minimum volume of water was added to a preparative sample of the product mixture, shaken at room temperature for two minutes and then rapidly filtered through filter paper using gravity filtration. The water was removed *in vacuo* on a rotary evaporator with the water bath temperature set at 60°. The yellow, brown oil which was obtained crystallized on standing at room temperature in less than five minutes. The ^{1}H NMR spectrum of the product confirmed its purity. This washing treatment was very effective in separating the product triester from unreacted 8-hydroxyquinoline and when it was repeated with the rate of cooling being slowed down significantly by simply holding the reaction flask after removal of water, two large crystals which were crystallographically suitable for an investigation were obtained.

6.3 SOLUTION AND REFINEMENT OF THE STRUCTURE

Accurate cell parameters were determined by a least-squares analysis of 24 reflections ($14 \leq Q \leq 15°$) on an Enraf Nonius CAD4 diffractometer using graphite monochromated MoKα (λ = 0.7107 Å) radiation and were collected by the ω-2Q scan technique. During the data collection, orientation of the crystal was monitored and 3 reference collections were periodically measured to check the stability of the crystal. Lorentz-polarization corrections were applied, but no absorption correction.

Inspection of the diffractometer data revealed systematic absences consistent with the space group $P2_1/c$.[95] This designation indicates a primitive lattice with a two-fold screw axis, conventionally taken as *b*, and a glide plane perpendicular to it with translation c/2. The equivalent positions x,y,z; $\bar{x},\bar{y},\bar{z}$; $\bar{x},y+\frac{1}{2},z-\frac{1}{2}$; and $x,\bar{y}-\frac{1}{2},z+\frac{1}{2}$ were therefore used in the subsequent solving and refining of the structure.

The crystal structure of dimethyl-(quinolin-8-yl) phosphate was solved by two methods:

1) In the first instance, trial structural information was obtained by locating the phosphorus atom in a Patterson map (also called an $|F|^2$ map). The equivalent positions for the space group $P2_1/c$ (mentioned above) were used to construct a Patterson grid (table 6.1) and the resulting 16 vectors (table 6.2) corresponded to the P-P interactions. The remaining non-hydrogen atoms were located in a subsequent difference map. The SHELX-76[96] programme system was used to generate the Patterson map.

2) The structure was also solved by the automatic centrosymmetric direct methods routine of the SHELX-S 84[97] programme system. An E-map yielded the positions of all seventeen non-hydrogen atoms, which were refined using SHELX 76.[96]

In the final refinement the non-hydrogen atoms were treated anisotropically. The hydrogen atoms were treated as follows: the methyl hydrogens were refined as a rigid group with a single temperature factor; the aromatic hydrocarbons constrained at 1.00 Å from their respective carbon atoms. Their positions being determined by the geometry of the molecule again, with a single temperature factor. The final refinement procedure gave a R-index of 0.0404 and a weighted R-index of 0.0368. In the final cycle of least-squares refinement, the average shift to error ratio was less than 1.0%. The difference electron-density map calculated after the final cycle of least-squares refinement revealed the maximum and minimum residual electron density as 0.24 and -0.27 $Å^{-3}$ respectively. The crystal data and experimental and refinement parameters for the structure determination are listed in table 6.3. An analysis of variance calculated after the final refinement is given in table 6.4. The final fractional coordinates and temperature factors* are given in tables 6.5, 6.6 and 6.7. The observed and calculated structural factors are given in Appendix II. The programme PARST[98] and XANADU[99] were used to calculate geometrical parameters and all molecular illustrations and parameters were performed by the programme PLUTO.[100]

* The anisotropic temperature factors have the following form:

$$T = \exp\left[-2\pi^2 (U11h^2a^{*2} + U22k^2b^{*2} + U331^2c^{*2} + 2U23klb^*c^* + 2U13hla^*c^* + 2U12hka^*b^*)\right]$$

Table 6.1 Patterson Grid for $P2_1/c$

	x, y, z	$\bar{x}, \frac{1}{2}+y, \frac{1}{2}-z$	$x, \frac{1}{2}-y, \frac{1}{2}+z$	$\bar{x}, \bar{y}, \bar{z}$
x, y, z	0 0 0	$2\bar{x}, \frac{1}{2}, \frac{1}{2}-2z$	$0, \frac{1}{2}-2y, \frac{1}{2}$	$2\bar{x}, 2\bar{y}, 2\bar{z}$
$\bar{x}, \frac{1}{2}+y, \frac{1}{2}-z$	$2x, \frac{1}{2}, \frac{1}{2}+2z$	0 0 0	$2x, 2\bar{y}, 2z$	$0, \frac{1}{2}-2y, \frac{1}{2}$
$x, \frac{1}{2}-y, \frac{1}{2}+z$	$0, \frac{1}{2}+2y, \frac{1}{2}$	$2\bar{x}, 2y, 2\bar{z}$	0 0 0	$2\bar{x}, \frac{1}{2}, \frac{1}{2}-2x$
$\bar{x}, \bar{y}, \bar{z}$	$2x, 2y, 2z$	$0, \frac{1}{2}+2y, \frac{1}{2}$	$2x, \frac{1}{2}, \frac{1}{2}+2z$	0 0 0

Table 6.2 Vectors and multiplicities obtained from Patterson Grid

Peaks	Multiplicity
0 0 0	4
$2x, \frac{1}{2}, \frac{1}{2}+2z$	2
$2\bar{x}, \frac{1}{2}, \frac{1}{2}-2z$	2
$0, \frac{1}{2}+2y, \frac{1}{2}$	2
$0, \frac{1}{2}-2y, \frac{1}{2}$	2
$2x, 2y, 2z$	1
$2\bar{x}, 2\bar{y}, 2\bar{z}$	1
$2x, 2\bar{y}, 2z$	1
$2\bar{x}, 2y, 2\bar{z}$	1

Table 6.3 Crystal data and experimental and refinement parameters for the structure determination

Crystal Data	
Molecular formula	$C_{11}H_{12}NO_4P$
Molecular weight	253.19 g mol^{-1}
Space Group	$P2_1/c$
a	13.604 (4) Å
b	7.509 (3) Å
c	13.093 (5) Å
β	116.56 (3)°
V	1 196.33 $Å^3$
Dc for z = 4	1.41 g cm^{-3}
μ (MoKα)	1.84 cm^{-1}
F (OOO)	528
Data Collection	
Crystal dimensions	0.16 x 0.38 x 0.50 mm
Scan mode	w - 2Q
Scan width	(0.93 + 0.35 tan Q)°
Aperture width	(1.45 + 1.05 tan Q) mm
Aperture length	4 mm
Range scanned	1 - 25° in Q
Stability of standard reflections	1.28%
Number of reflections collected	1 781
Number of observed reflections	1 377 with $I(rel) > 2\sigma I(rel)$
Final Refinement	
Number of variables	162
$R = \Sigma\|\|Fo\| - \|Fc\|\|/\Sigma\|Fo\|$	4.04%
$R_w = \Sigma w^{\frac{1}{2}}\|\|Fo\| - \|Fc\|\|/\Sigma w^{\frac{1}{2}}\|Fo\|$	3.68%
Weighting scheme, w	$(\delta^2 F)^{-1}$
U (methyl H)	0.15 (1)
U (aromatic H)	0.052 (4)

Table 6.4 Analysis of Variance[a]

(a) By parity groups

Group	GGG	UGG	GUG	UUG	GGU	UGU	GUU	UUU	All
N	197	187	168	170	159	147	158	151	1337
V	92	96	75	78	72	80	102	74	85

(b) As a function of sin θ

Sin θ	0	.18	.23	.26	.29	.31	.34	.36	.38	.40	.43
N	147	143	121	157	104	193	123	117	112	120	
V	158	114	67	67	60	67	63	55	53	56	

(c) As a function of $\sqrt{F/F_{max}}$

$\sqrt{F/F_{max}}$	0	.19	.22	.24	.26	.28	.31	.34	.39	.45	1.00
N	139	154	147	140	110	146	109	131	143	118	
V	59	63	6!	69	65	79	81	78	85	169	

(d) As a function of |Miller Index|

|h|	0	1	2	3	4	5	6	7	8	9	10	11	12	13	Rest
N	76	128	129	117	120	116	126	101	92	83	76	59	51	38	25
V	150	105	87	81	81	88	78	81	62	55	54	75	66	61	64

|k|	0	1	2	3	4	5	6	7	8	9	10	11	12	13	Rest
N	132	240	231	216	193	127	115	64	19	0	0	0	0	0	0
V	119	109	95	69	65	58	51	53	54	0	0	0	0	0	0

|ℓ|	0	1	2	3	4	5	6	7	8	9	10	11	12	13	Rest
N	69	129	140	122	127	110	123	96	121	82	84	45	40	26	23
V	101	123	81	78	99	70	93	74	73	55	77	60	64	46	77

[a] N = Number of reflections in the group; $V = 100\,[M(\Sigma \underline{w}|F_o - F_c|^2)/N\Sigma \underline{w}]$;

M = Total number of reflections.

Table 6.5 Fractional atomic coordinates (x 10^4) of the non-hydrogen atoms with e.s.d.'s in parentheses

	x/a	y/b	z/c
P (1)	3 370 (1)	1 474 (1)	1 082 (1)
N (1)	827 (2)	-1 376 (4)	-462 (2)
O (1)	4 370 (2)	2 006 (4)	1 038 (2)
O (2)	2 992 (2)	-508 (3)	752 (2)
O (3)	2 314 (2)	2 508 (3)	272 (2)
O (4)	3 383 (2)	1 631 (4)	2 275 (2)
C (1)	-201 (3)	-1 823 (5)	-1 053 (3)
C (2)	-661 (3)	-2 493 (5)	-2 183 (3)
C (3)	1 (3)	-2 697 (5)	-2 689 (3)
C (4)	1 116 (3)	-2 261 (5)	-2 101 (3)
C (5)	1 872 (3)	-2 468 (5)	-2 560 (3)
C (6)	2 940 (3)	-2 033 (5)	-1 945 (3)
C (7)	3 329 (3)	-1 331 (5)	- 839 (3)
C (8)	2 617 (3)	-1 123 (4)	- 379 (3)
C (9)	1 502 (3)	-1 586 (5)	- 972 (3)
C (31)	2 332 (5)	4 404 (6)	163 (4)
C (32)	4 373 (4)	1 561 (8)	3 316 (3)

Table 6.6 Fractional atomic coordinates (x 10^4) of the hydrogen atoms with e.s.d.'s in parentheses.

	x/a	y/b	z/c
H(1)	-702 (3)	-1676 (5)	-686 (3)
H(2)	-1458 (3)	-2812 (5)	-2592 (3)
H(3)	-304 (3)	-3160 (5)	-3488 (3)
H(5)	1612 (3)	-2951 (5)	-3350 (3)
H(6)	3464 (3)	-2207 (5)	-2283 (3)
H(7)	4118 (3)	-984 (5)	-396 (3)
H(311)	1607 (5)	4845 (6)	-431 (4)
H(312)	2931 (5)	4822 (6)	-24 (4)
H(313)	2462 (5)	4878 (6)	927 (4)
H(321)	4220 (4)	1894 (8)	3972 (3)
H(322)	4869 (4)	2470 (8)	3232 (3)
H(323)	4735 (4)	367 (8)	3463 (3)

Table 6.7 Temperature Factors ($Å^2$ x 10^3) of all atoms with e.s.d.'s in parentheses

	U11	U22	U33	U23	U13	U12
P(1)	35 (1)	45 (1)	35 (1)	-7 (1)	15 (0)	-6 (1)
N(1)	41 (2)	41 (2)	36 (2)	-2 (2)	23 (1)	-2 (2)
O(1)	48 (2)	78 (2)	77 (2)	-26 (2)	38 (2)	-25 (2)
O(2)	47 (2)	44 (2)	23 (1)	0 (1)	13 (1)	-2 (1)
O(3)	48 (2)	44 (2)	57 (2)	4 (1)	15 (1)	1 (2)
O(4)	58 (2)	85 (2)	35 (2)	-18 (2)	21 (1)	-12 (2)
C(1)	44 (2)	51 (3)	56 (2)	2 (2)	31 (2)	-2 (2)
C(2)	35 (2)	56 (3)	55 (3)	-13 (2)	15 (2)	-10 (2)
C(3)	50 (3)	43 (2)	37 (2)	-11 (2)	14 (2)	-3 (2)
C(4)	38 (2)	34 (2)	30 (2)	- 4 (2)	13 (2)	1 (2)
C(5)	55 (3)	54 (3)	34 (2)	-8 (2)	24 (2)	3 (2)
C(6)	52 (3)	61 (3)	46 (2)	-8 (2)	32 (2)	4 (2)
C(7)	34 (2)	52 (3)	43 (2)	-1 (2)	17 (2)	0 (2)
C(8)	39 (2)	31 (2)	24 (2)	1 (2)	11 (2)	1 (2)
C(9)	37 (2)	27 (2)	29 (2)	2 (2)	15 (2)	2 (2)
C(31)	106 (4)	36 (3)	90 (4)	5 (3)	29 (3)	5 (3)
C(32)	88 (4)	131 (5)	35 (3)	-12 (3)	6 (3)	-8 (4)

H_{ring} U_{iso} 52 (4)

H_{methyl} U_{iso} 152 (10)

6.4 DISCUSSION

A perspective view of the compound indicating the atomic nomenclature is given in fig. 6.1. Illustrative projections of the crystal packing are shown in fig. 6.2 and 6.3. The interatomic bond lengths are given in table 6.8 and the bond angles are listed in table 6.10a and 6.10b.

The X-ray crystal structure determination of dimethyl-(quinolin-8-yl) phosphate indicates that the methyl group nearest to the quinolyl nitrogen is distorted not only above the plane of the aromatic system but away from the nitrogen atom. Although the perpendicular distance of C31 from the least squares plane containing the nitrogen atom is 3.31Å (calculated using XANADU), no N···CH_3 intramolecular non-bonding distance is reported in the final output for the inter-atomic contacts (the upper limit for these contacts was set at the reasonable value of 3.50Å). We can therefore conclude that the nitrogen - (methyl) carbon intramolecular distance is much greater than the corresponding sum of the van der Waals radii. These results are in agreement with our conclusions pertaining to the isomerisation of the substrate to the zwitterion in solution. Since the molecular geometry of the ester does not favour intramolecular N···CH_3 interactions, the methyl transfer reaction occurs *via* the bimolecular mechanism.

In order to see whether a crystal of the ester (C) could serve as a model for the bimolecular methyl group transfer, the intermolecular relations between ring nitrogen and methyl ester groups had to be examined. Selected non-bonding distances from the nitrogen atom are listed in table 6.9. The non-bonded intermolecular

N(1)····C(31') distance (symmetry translation x, y-1, z applied to C(31')) is 3.661 Å, and the N(1)··C(31') - O(3') angle is 148°. The alignment of the NCO system is identical to that obtained[94] for methyl p-(dimethylamino)benzenesulfonate (147°), but the non-bonded N···C' distance is significantly longer than that of 3.54 Å reported[94] for the intermolecular $Me_2N\cdots MeO_3S$ interactions. Since the sum of the van der Waals radii for C and N is 3.50 Å, it seems that in the sulfonate case, the nucleophilic and electrophilic centres are located just at the borderline of bonding interactions (*ca.* 1% in excess of the corresponding sum of the van der Waals radii), while in our case the extra distance of *ca.* 0.16 Å is as much as *ca.* 5% in excess.

Although the title compound isomerises completely to the zwitterion in aqueous solution (ch. 5.2) or as a melt at 120°C after *ca.* 2 days, we did not observe any reaction occurring in the solid state. The crystals were heated to just below the melting point (50°C) for 26 days after which time the ^1H NMR spectrum showed no indication of the methyl group transfer. Close examination of the crystal structures of the two esters discussed, led us to the opinion that it is the detailed geometry of the intermolecular relationship of the nucleophilic → electrophilic centers, not just the non-bonded distance, which is responsible for the occurrence (or absence) of a solid state reaction.

In methyl p-dimethylaminobenzenesulfonate, the nitrogen non-bonding electrons occupy the $2p_z$ atomic orbital which is perpendicular to the plane of the ring and its substituents. For the reaction to occur, the intermolecular angle between the $C_{(ipso)}$-N bond and the

N···CH_3^1 group should have a value of 90°, and as the reaction progresses, this angle should change to the tetrahedral value of 109.5°. The value of this angle calculated from the reported data is 105.6°, which means that the two molecules in the crystal lattice can be taken as a point "mapping" the reaction coordinate (fig. 6.4a).

Dimethyl-(quinolin-8-yl) phosphate represents an entirely different system. In this compound it is the sp^2 hybridised nitrogen atomic orbital which is responsible for the observed nucleophilic properties, and it is located in the plane of the heterocyclic ring. For the S_N2 methyl transfer reaction the adjacent methyl group should be located on the same plane, and the angle between the C(2)-N (or C(9)-N) bond and the N····CH_3^1 direction should be (and should remain) 120°. The crystal structure of the title compound does not, however, meet, even approximately, these conditions (fig. 6.4b). The methyl group is not only located 3.31 Å above the plane of the ring, but it is also shifted considerably with respect to the C(4)····N axis, so the two angles involving atoms C(2), C(9), N and CH_3^1 are not 120°, but 104.7° and 65°, respectively. For the nigrogen atom to approach the O-methyl group of another molecule of the substrate in order to achieve the methyl group transfer, severe distortions of both molecules in their crystal lattice would be necessary. The importance of the angular orientation of the orbitals involved in a reaction occurring in the solid state was noted before. For example, in methyl m-bromocinnamate, the centre to centre distance of the alkene C=C groups in glide-plane related molecules is short (3.93 Å); however, the double bonds are not parallel. As a consequence, this

compound is essentially unchanged after irradiation over long periods, during which other cinnamic deviatives have completely dimerised to the cyclobutane system.[101]

The intramolecular nitrogen-phosphorus non-bonded distance in phosphate C is 3.79 Å which is 0.35 Å greater than the sum of the van der Waals radii of 3.44 Å. This observation immediately supports our proposals that the quinolyl nitrogen atom is not sensitive to intramolecular interactions and it contrasts with the N···P non-bonded distance of 3.02 Å reported for the bis-(p-nitrophenyl) analogue.[41] In the latter case, the presence of a good leaving group (p-nitrophenoxy) enhances the electrophilicity at the phosphorus atom and this in turn promotes intramolecular nitrogen → phosphorus interaction. No such effect is operable with methyl ester substituents. The difference in leaving ability of the p-nitrophenoxy and methoxy groups, as measured by the pK_a values of the respective conjugate acids, is of the order of 10^9.[102]

The P-O(3) bond length is identical to the P-O(4) bond length (1.559(3) Å) which indicates that there is no tendency for one of the methoxy groups to adopt an apical position leading to a trigonal bipyramidal geometry. As anticipated the P-O(2) bond is slightly longer than the P-OMe bonds (by 0.012(3) Å) due to the more electron withdrawing nature of the quinolyl ring as compared to the dimethyl substituents. The P=O bond is characteristically insensitive to changes in the substituent electron releasing or electron withdrawing ability[103] and the final observed distance of 1.444(3) Å is as expected.

In conclusion then, the crystal structure of (C) provides no evidence for any significant interactions between the ring nitrogen and such electrophilic centres, as intramolecular phosphoryl (because no good leaving group is present at P atom), intramolecular methyl (presumably because of the steric requirements of a seven-membered ring), and the methyl group of the adjacent molecule (as a result of the crystal packing pattern).

The geometry at the phosphorus atom approaches that of the regular tetrahedron. Table 6.10a lists all the O-P-O angles for dimethyl-(quinolin-8-yl) phosphate and the average value for these angles is 109.1°. However, the individual O-P-O angles show a fairly considerable deviation from the mean value (5.3 - 7.8) and the six angles can be clearly divided into two groups: three "large" [115.5 (2) - 116.7 (2)°] and three "small" [101.3 (2) - 103.8 (2)°]. The "narrow" bond angles are characteristically between the three ester bonds.[104] Distortion of the tetrahedral geometry at phosphorus is typical for P^{IV} derivatives of the general formula ABCP=Y and furthermore, these observed deviations are similar to those recently reported for bis-(p-nitrophenyl)-quinolin-8-yl phosphate.[41] Additional bond angles are listed in table 6.10b.

The plananity of the N(1) C(1) C(2) C(3) C(4) C(9) fragment (plane 1), the C(4) C(5) C(6) C(7) C(8) C(9) fragment (plane 2) and the N(1) C(1) C(2) C(3) C(4) C(5) C(6) C(7) C(8) C(9) fragment (plane 3) is summarized in table 6.11a. The minimal deviation of the atoms from the least squares planes and the angle between the normals to the least squares planes (table 6.11b) indicate that all three groups of atoms do not deviate significantly from plananity.

Figure 6.1 Perspective view of the molecule and atomic nomenclature.

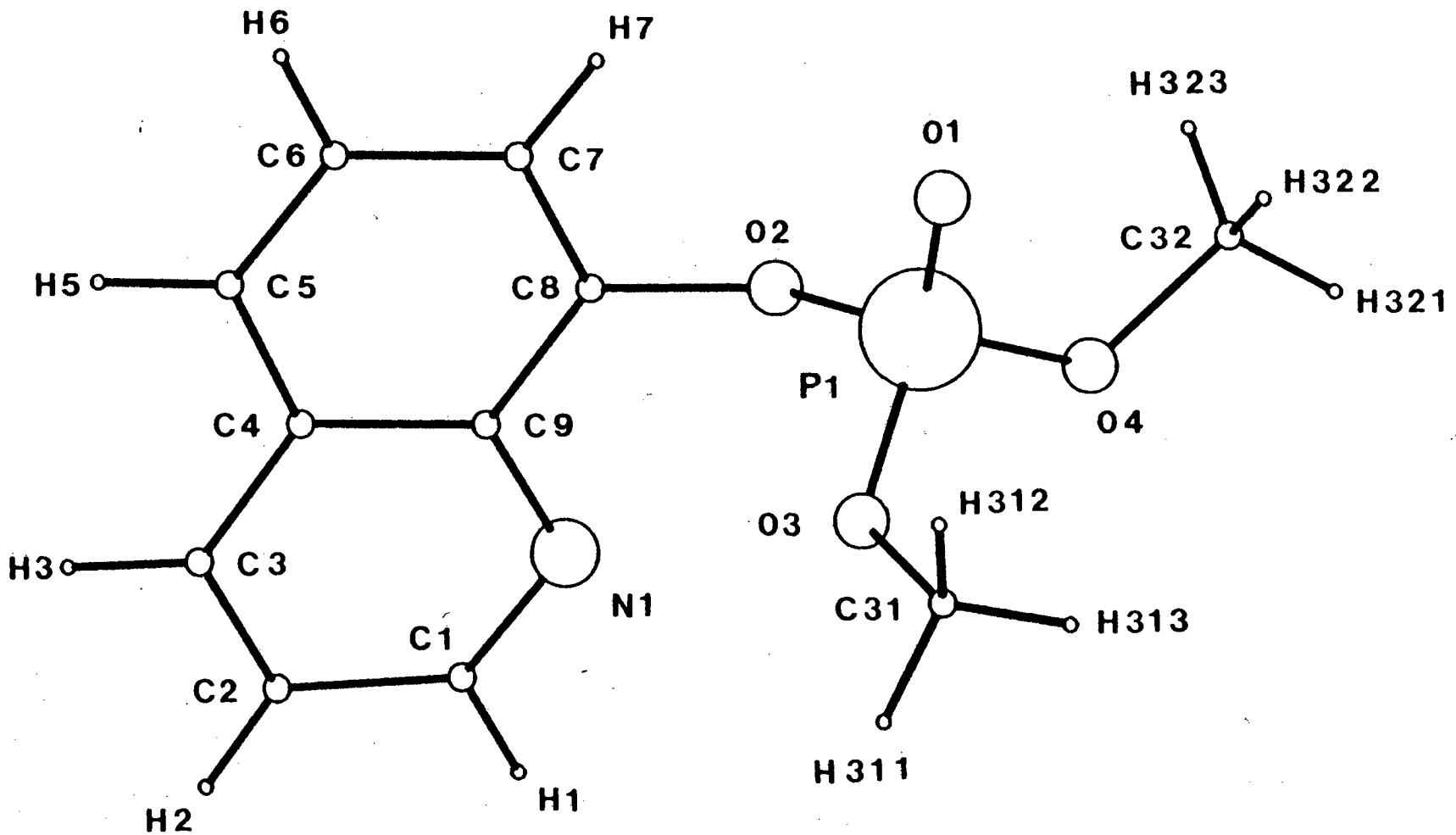


Figure 6.2 Projection of the crystal packing down the *b* axis

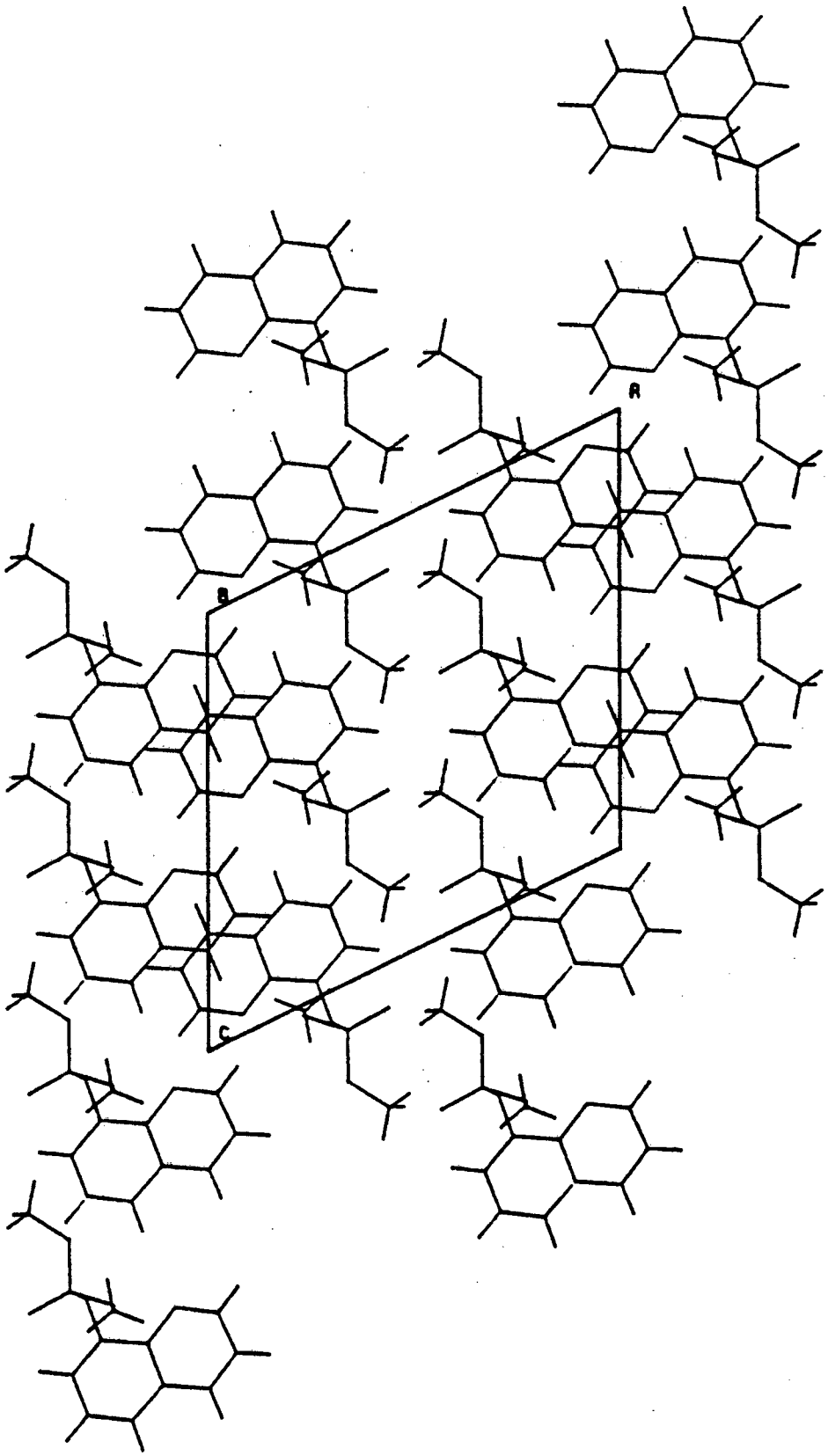


Figure 6.3 Projection of the crystal packing down the *a* axis.

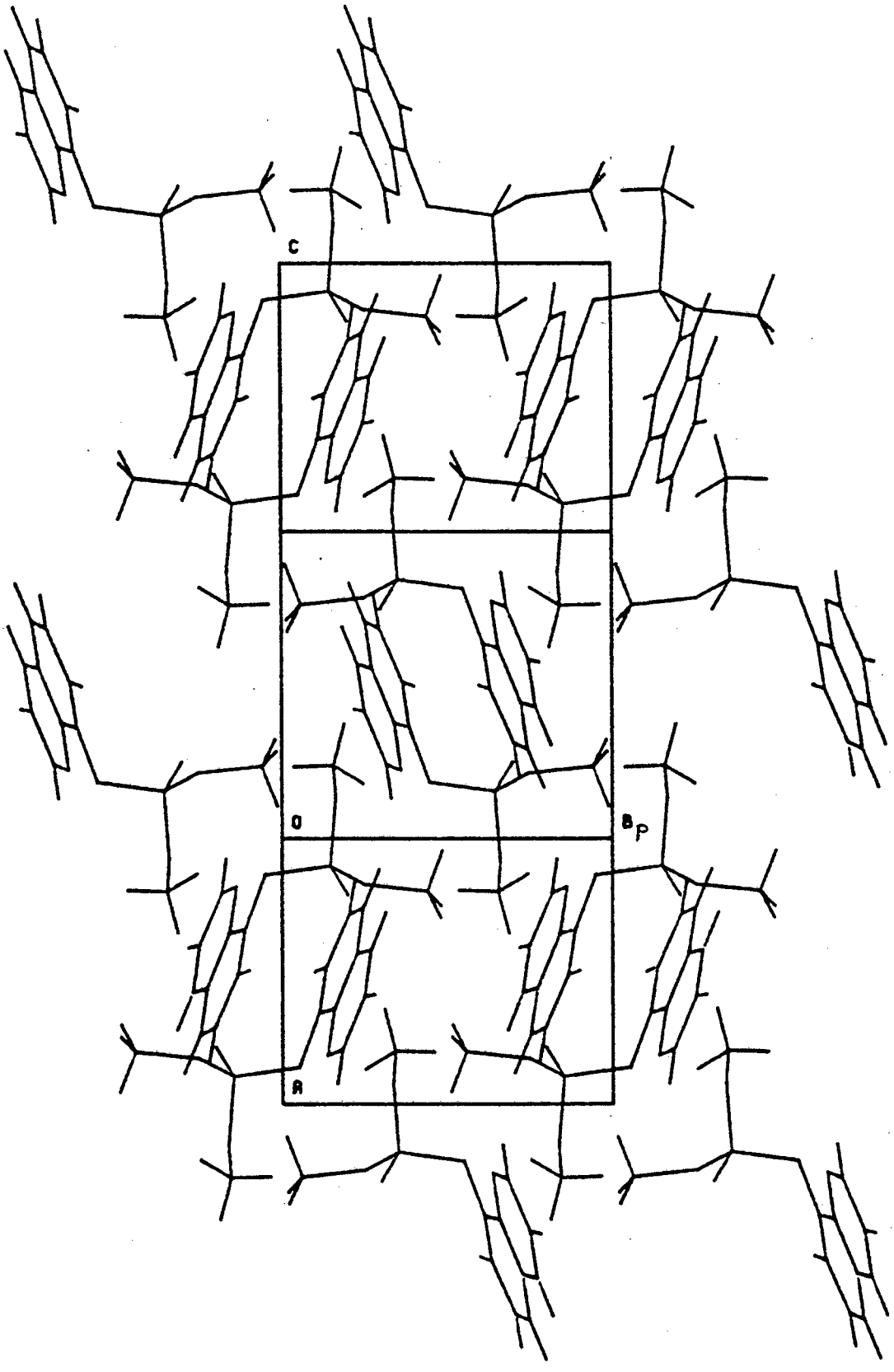
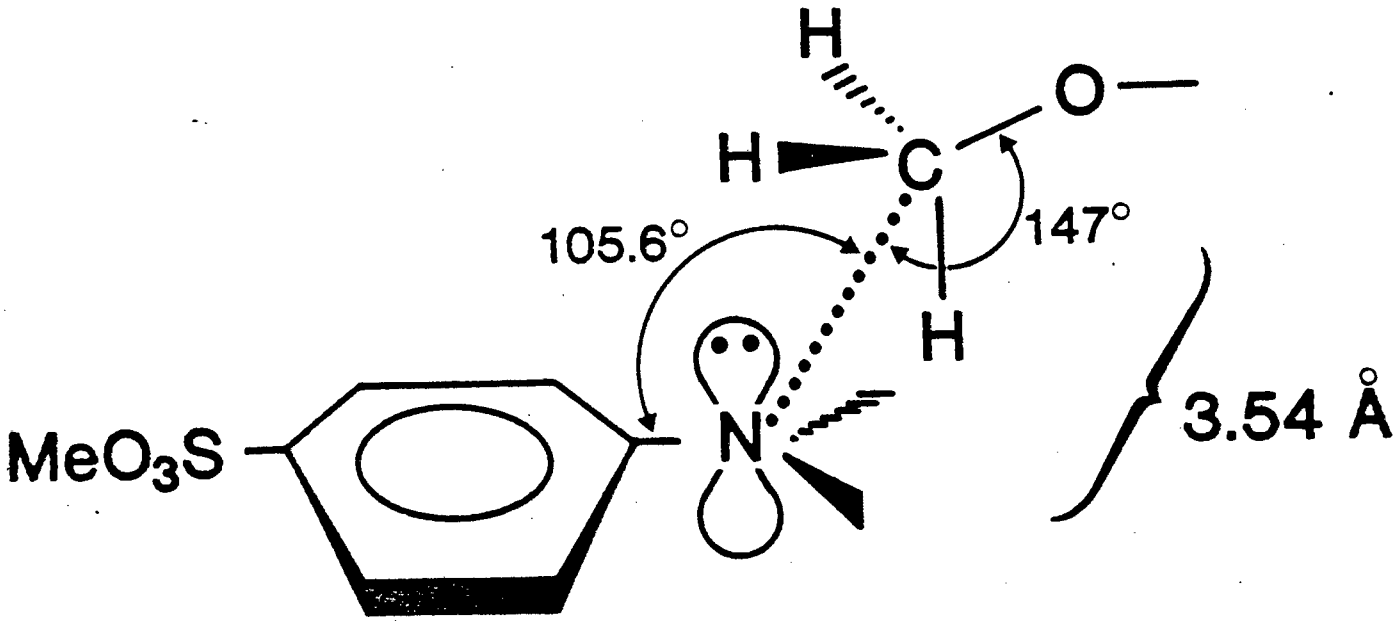
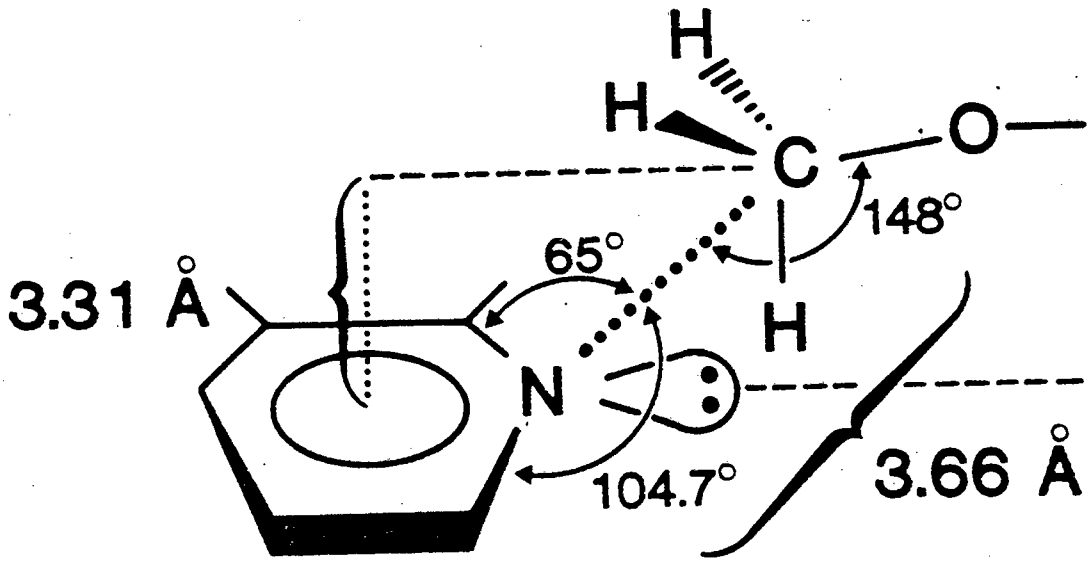


Figure 6.4 Intermolecular nitrogen-methyl relations in:
a) methyl 4-dimethylaminobenzenesulfonate, and
b) dimethyl-(quinolin-8-yl) phosphate.
A perspective view.



(a)



(b)

Table 6.8 Bond lengths (Å) with e.s.d.'s in parentheses

P(1)-O(1)	1.444 (3)
P(1)-O(2)	1.571 (3)
P(1)-O(3)	1.559 (3)
P(1)-O(4)	1.559 (3)
N(1)-C(1)	1.304 (4)
N(1)-C(9)	1.365 (6)
C(1)-C(2)	1.416 (5)
C(2)-C(3)	1.344 (7)
C(3)-C(4)	1.399 (5)
C(4)-C(5)	1.413 (7)
C(4)-C(9)	1.423 (5)
C(5)-C(6)	1.349 (5)
C(6)-C(7)	1.403 (5)
C(7)-C(8)	1.359 (7)
C(8)-C(9)	1.404 (5)
C(8)-O(2)	1.411 (4)
O(3)-C(31)	1.432 (5)
O(4)-C(32)	1.426 (4)

Table 6.9 Selected Nitrogen non-bonded distances.[a]

Interatomic contacts		
N(1)···P(1)	3.792	
N(1)···O(3)	3.433	(4)
N(1)···O(4)	4.346	
Intermolecular contacts[b]		
N(1)···C(31')	3.661	
N(1)···H(311')	3.024	(6)
N(1)···H(312')	3.898	
N(1)···H(313')	3.543	

[a]Only contacts less than 3.50 Å report e.s.d.'s.

[b]Symmetry translation x, y-1, z applied to second atom.

Table 6.10a Selected bond angles (°) with e.s.d.'s in parentheses

O(1)-P(1)-O(2)	116.7 (2)
O(1)-P(1)-O(3)	115.7 (2)
O(1)-P(1)-O(4)	115.5 (2)
O(2)-P(1)-O(3)	101.3 (2)
O(2)-P(1)-O(4)	101.7 (2)
O(3)-P(1)-O(4)	103.8 (2)

Table 6.10b Additional bond angles (°) with e.s.d.'s in parentheses

P(1)-O(2)-C(8)	121.3 (2)
P(1)-O(3)-C(31)	120.8 (3)
P(1)-O(4)-C(32)	122.5 (3)
N(1)-C(1)-C(2)	124.6 (4)
N(1)-C(9)-C(8)	122.2 (4)
N(1)-C(9)-C(4)	119.9 (3)
C(1)-N(1)-C(9)	117.2 (3)
C(1)-C(2)-C(3)	118.4 (4)
C(2)-C(3)-C(4)	120.2 (4)
C(3)-C(4)-C(5)	123.8 (4)
C(3)-C(4)-C(9)	117.5 (4)
C(4)-C(5)-C(6)	120.9 (4)
C(4)-C(9)-C(8)	117.9 (4)
C(5)-C(4)-C(9)	118.7 (4)
C(5)-C(6)-C(7)	121.0 (4)
C(6)-C(7)-C(8)	119.1 (4)
C(7)-C(8)-O(2)	120.5 (4)
C(7)-C(8)-C(9)	122.3 (4)
C(9)-C(8)-O(2)	117.1 (4)

Table 6.11a Angle between normals to least squares planes (as defined on page 201) with e.s.d.'s in parentheses

Plane 1 - Plane 2	1.02° (1)
Plane 1 - Plane 3	0.50° (1)
Plane 2 - Plane 3	0.52° (1)

Table 6.11b Maximum deviations of the atoms from least squares planes

Plane 1	< 0.005 Å
Plane 2	< 0.009 Å
Plane 3	< 0.02 Å

Chapter 7

Mass Spectrometry of Dimethylaryl , Dimethyl(arylalkyl) Phosphates and Related Acetates

7.1 INTRODUCTION

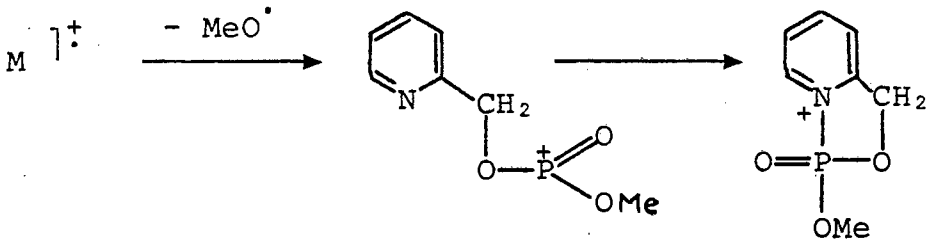
Besides work on the mass spectral fragmentation behaviour of organic pesticides, which includes substituted phosphates and thionophosphates,[105] a survey of the literature revealed that relatively little work on the mass spectra of mixed phosphate triesters has been published. Generally though, the mass spectra of triaryl phosphates[106] and trialkyl phosphates[106] are characterized by extensive rearrangement processes. In the first case these fragmentations often involve expulsion of the phosphorus atom and recombination of the aromatic nuclei with or without oxygen bridges.

An investigation of the fragmentation behaviour of the phosphate esters A - D was carried out with the aim of firstly, further characterizing the four triesters and secondly, establishing the role (if any) played by the nitrogen heteroatom in the dynamics of the gas phase behaviour of this group of compounds.

7.2 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(2-PYRIDYLMETHYL) PHOSPHATE, A

The main ions formed in the mass spectrum (fig. 7.1) of dimethyl-(2-pyridylmethyl) phosphate are listed in table 7.1.

The molecular ion (m/e 217) was observed and it was proposed that loss of methoxy radical occurred to give the phosphorylium ion at m/e = 186. We believe that this phosphorylium ion so formed can be stabilized by resonance involving the pyridyl nitrogen atom.

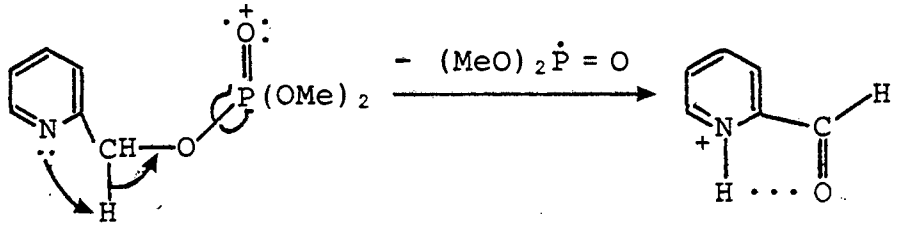


(7.1)

m/e 186

This postulate is not an entirely new idea and the same type of internal stabilization of the phosphorylium ion has recently been proposed in the fragmentation of (2-pyridylmethyl)-bis-(p-nitrophenyl) phosphate.[16a]

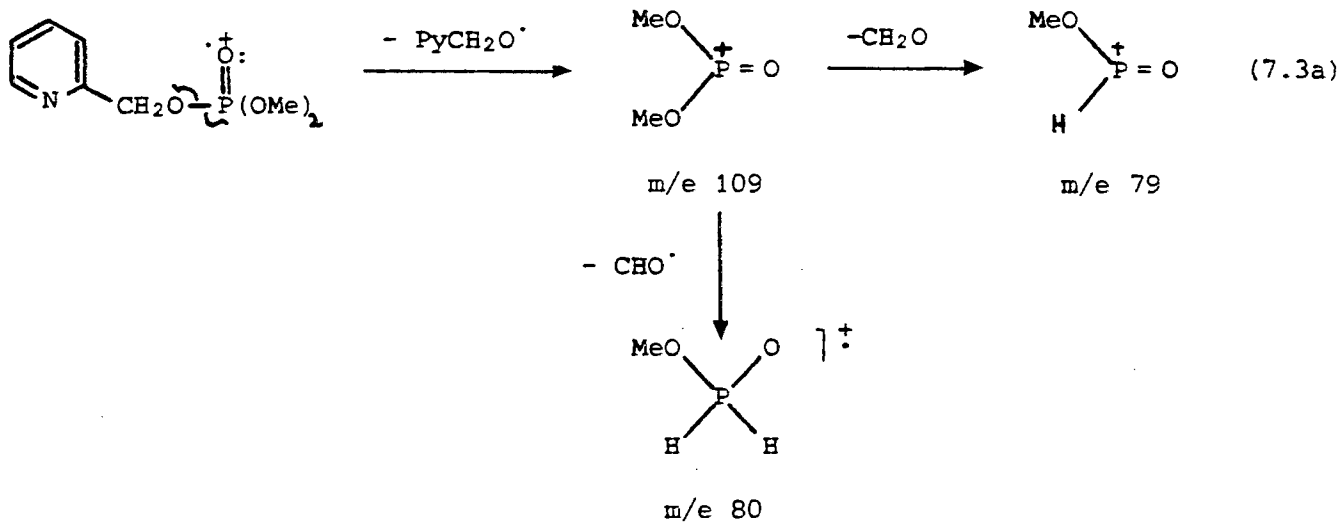
The base peak at m/e = 108 which corresponds to the formula C_6H_6NO, was attributed to protonated 2-pyridylmethanal. This was postulated as forming directly from the molecular ion with hydrogen ion migration accompanying the release of the dimethylphosphoranyl radical species, $(MeO)_2\dot{P}{=}O$, as shown in eq. 7.2. This results in a very stable $2\pi/6\pi$ conjugated system which can be further stabilized by hydrogen bonding (structure 7.1).



(7.2)

7.1 m/e 108

The fragment at m/e = 109 (relative intensity 22%) can be assigned to the phosphorylium ion resulting from homolytic CH_2O-P bond cleavage and requires the loss of the $PyCH_2O^{\cdot}$ radical species (eq. 7.3a). The peak at m/e 79 then arises by loss of formaldehyde. Expulsion of $CHO^{\cdot}$ radical from m/e 109 (eq. 7.3b) is also possible and gives rise to m/e 80.[109] We feel confident that peaks at m/e 79 and 80 can be assigned to $CH_4O_2P^+$ and $CH_5O_2P^+$, respectively, rather than to PO_3^+ and HPO_3^+, as reports from the literature reveal that mass measurements on m/e 79 and 80 in trimethyl phosphate[108] and trimethyl phosphite,[110] show that these masses do indeed arise from the former pair of ions.

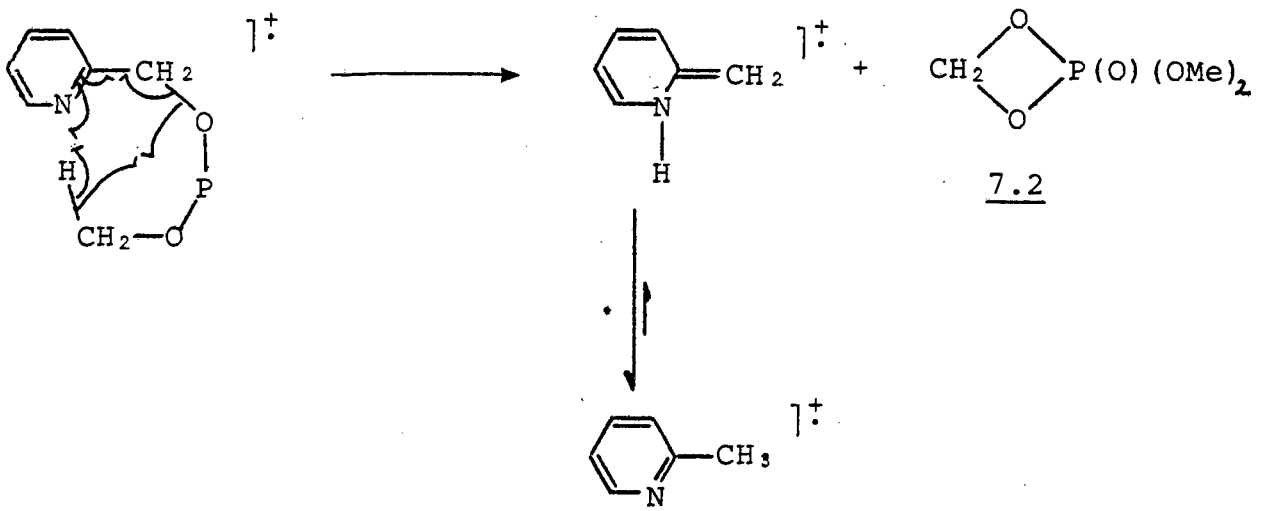


(7.3a)

(7.3b)

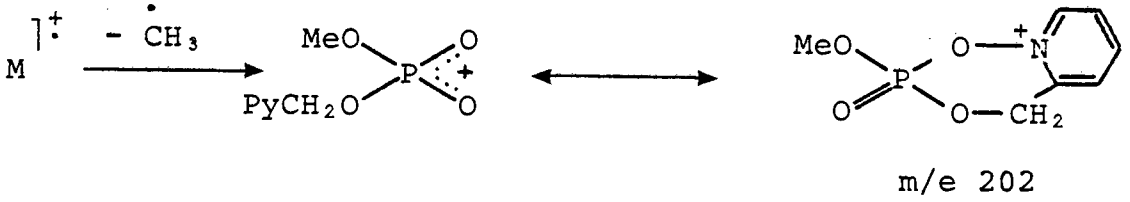
The peak at m/e 93 (relative intensity = 17%) results from cleavage of the $PyCH_2$-O bond, accompanied by hydrogen migration. We believe that hydrogen transfer occurs from the methyl ester substituent to the pyridyl nitrogen and can be represented by scheme 7.1.

Scheme 7.1



The products of this fragmentation are α-picoline and the methyl methylene phosphate species 7.2. The phosphite analogue of 7.2 has recently been implied during the fragmentation of some secondary phosphoramidates.[111,112] Although the species 7.2 is not known, it is the synthetic difficulties rather than any intrinsic lack of stability that makes these types of compounds inaccessible.

Minor, but interesting, is the fragmentation consisting of loss of methyl radical from the molecular ion to give the peak at m/e 202 (relative intensity 3%). Since the analogous O-C bond cleavage yielding the 2-pyridylmethyl radical (obviously more stable than the methyl radical) and the corresponding ion at m/e 125 occurs to a much lower degree (if at all), it seems that the positive charge developed in the fragmentation $M^{+\cdot} \rightarrow CH_3^{\cdot}$ + m/e 202, can be stabilized by the pyridine group, as envisaged in eq. 7.4.



m/e 202

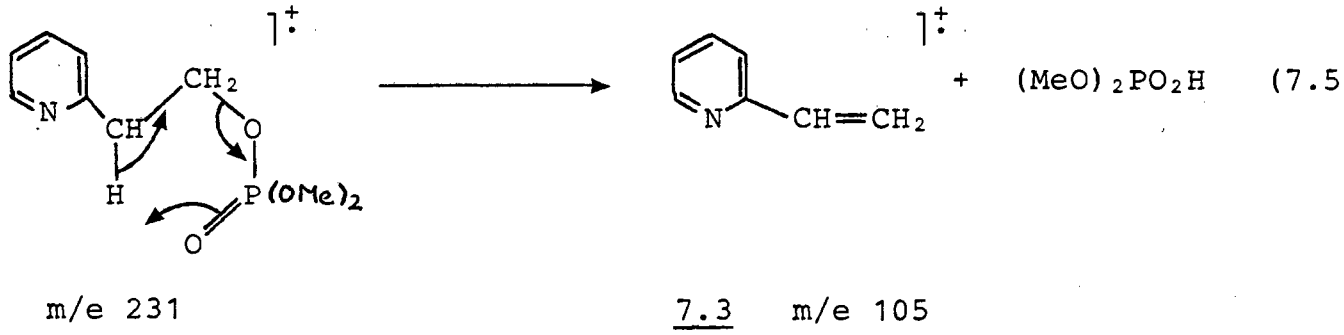
(7.4)

Interestingly, no ($M - CH_3^{\cdot}$) peak is observed in the mass spectrum of trimethyl phosphate,[108] and this fact tends to support the stabilization of the positive charge by the pyridyl nitrogen as shown in eq. 7.4.

7.3 FRAGMENTATION BEHAVIOUR OF DIMETHYL-[β-(2-PYRIDYLETHYL)] PHOSPHATE, B

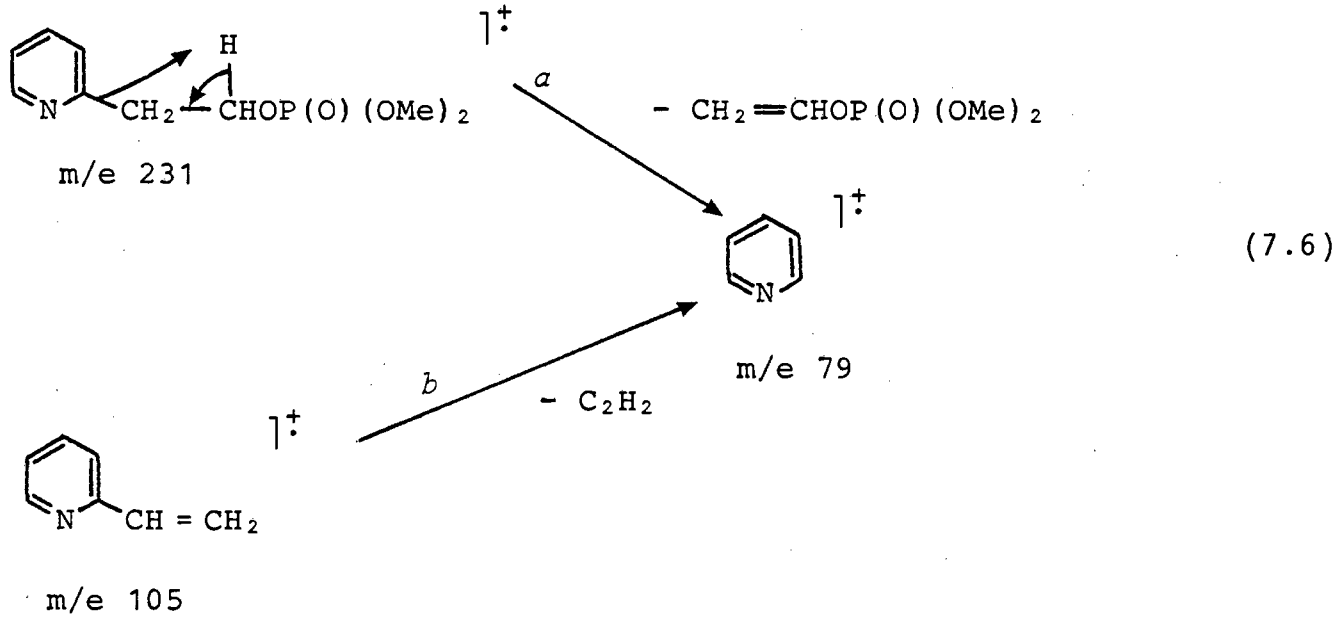
The mass spectrum (fig. 7.2) of the product confirms its structure and provides information about its fragmentation pathways. All ions of significance are indicated in table 7.2.

The molecular ion peak (m/e 231) was observed but was of low intensity (4% relative abundance). The major fragments present were those corresponding to the base peak (m/e 105) and to another peak at m/e 79 with a relative abundance of 76% of the base peak. The base peak formation is attributed to an elimination reaction following the McLafferty rearrangement mechanism[20] as shown in eq. 7.5. The McLafferty rearrangement in this case should be particularly favoured since it yields a resonance-stabilized alkene (7.3).



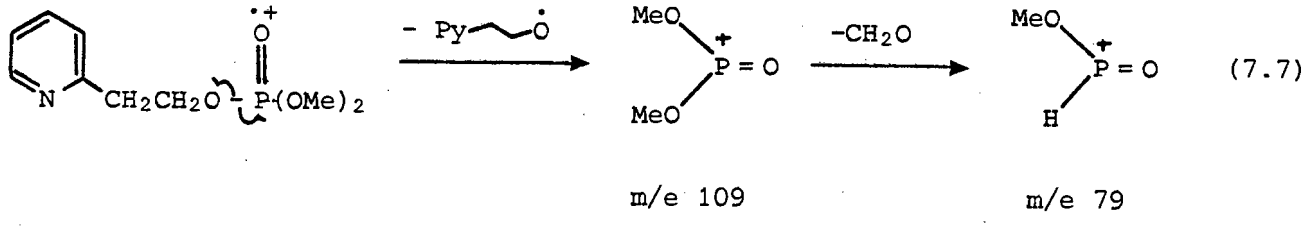
m/e 231 — 7.3 — m/e 105 (7.5)

The fragment at m/e 79 can be attributed to the radical ion of pyridine or to the $CH_4O_2P^+$ species. In the former case, the radical ion of pyridine is postulated as forming *via* one or two mechanisms, both involving C-C bond cleavage and hydrogen migration to the pyridine ring. Firstly, dimethylvinyl phosphate is eliminated from the molecular ion (pathway *a*, eq. 7.6) and secondly, the alternate pathway (*b*) requires loss of acetylene from the molecular ion of 2-vinylpyridine.



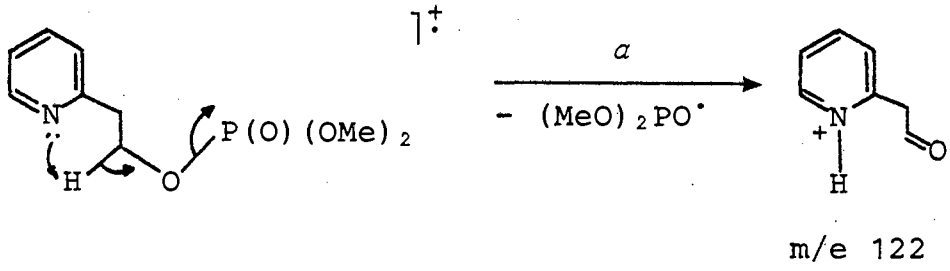
(7.6)

The fragment ion at m/e 79 can also arise by simple homolytic P-O bond cleavage from the parent-molecule ion to give the dimethyl phosphorylium ion, m/e 109, followed by further elimination of CH_2O (eq. 7.7). This is analogous to the formation of the peak at m/e 109 in the spectrum of the 2-pyridylmethyl isomer (see eq. 7.3a).

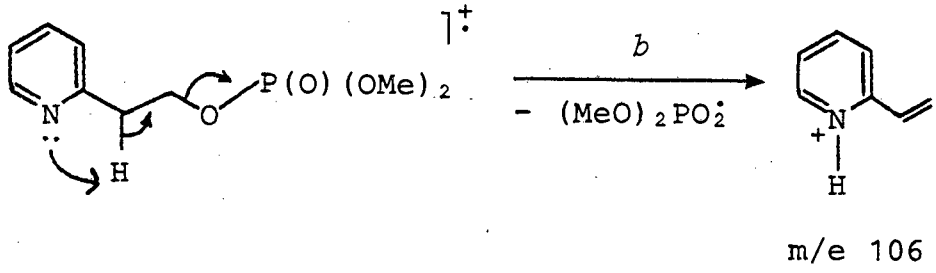


We suspect that the intensity of the m/e 79 fragment ion, 76%, for dimethyl-[β-(2-pyridylethyl)] phosphate as compared to the intensity of this fragment ion, 12%, in dimethyl-(2-pyridylmethyl) phosphate, lends support for eq. 7.6 to more than account for this fragment ion. In fact, a fragment at m/e 79 is the most abundant in the mass spectrum of 2-vinylpyridine itself.[113]

As far as the fragmentation involving hydrogen abstraction by the heterocyclic nitrogen atom is concerned, the 2-pyridylethyl substrate, when compared with the 2-pyridylmethyl derivative, can follow two, not one, reaction pathways. One, analogous to that presented by eq. 7.2, proceeds with the abstraction of the β-hydrogen and involves the P-O bond cleavage (pathway *a*, eq. 7.8). Another can be described as α,β-elimination, yielding an oxygen-derived radical and the 2-vinylpyridinium species (pathway *b*, eq. 7.8).



(7.8)



The competing fragmentation (pathway *b*) is responsible for the much lower yield of the ion at m/e 122 (15%) when compared with that of its analogue m/e = 108 (base peak).

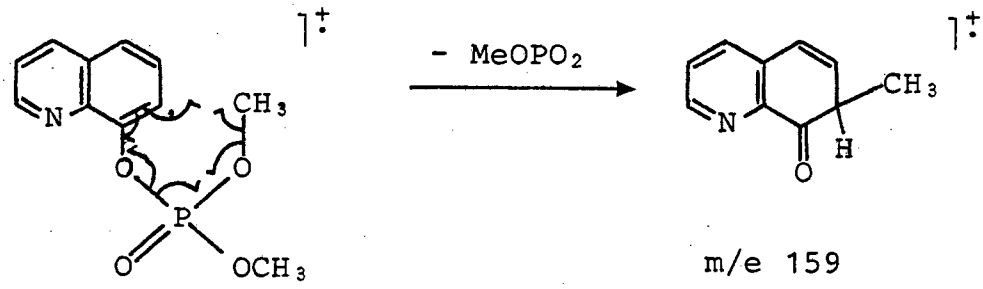
7.4 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(QUINOLIN-8-YL) PHOSPHATE, C

The mass spectrum of dimethyl-(quinolin-8-yl) phosphate is shown in fig. 7.3. Table 7.3 lists the main ions formed and scheme 7.2 outlines the proposed fragmentation pattern.

The most striking feature of the mass spectrum of this compound compared to that of its 2-pyridylmethyl and 2-pyridylethyl analogues (A and B, respectively), is the intensity of the molecular ion. Analogous with the mass spectrum of compound A, is the loss of a

methoxy radical to give a phosphorylium ion which can be stabilized by resonance (pathway *a* in scheme 7.2). It is perhaps merely coincidental that the relative intensity of the fragment arising from loss of methoxy radical from the molecular ion in A and C, is *ca.* 20% in both cases.

The fragment ion at m/e 159 results from the loss of methyl metaphosphate, accompanied by methyl group migration from the ester oxygen to the quinolyl skeleton. The proposed mechanism of this fragmentation is presented in eq. 7.9.

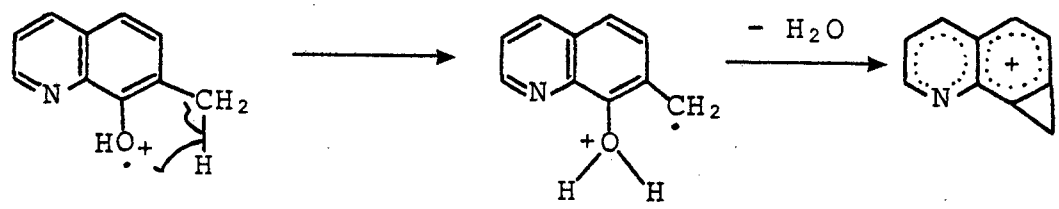


m/e 159 (7.9)

Fragmentations which involve phosphate ester group migration and expulsion of a metaphosphate species, $X\text{-}PO_2$ are common for a variety of organophosphorus derivatives. The fragmentation presented in eq. 7.9 has its analogy in the mass spectra of phosphoric amidoesters, where the migration of an R group from oxygen to nitrogen was observed, giving rise to metaphosphate and amine fragmentation products.[112] Further loss of a hydrogen atom generates the base peak at m/e 158. This fragmentation is favoured as the resulting ion can be stabilized by charge delocalization over the nitrogen and oxygen atoms as shown by pathway *b* in scheme 7.2. A similar $O\text{-}C_{AR}$ methyl migration has been observed in the mass spectrum of 1-napthyl-dimethyl phosphate.[114] However, no further loss of a hydrogen radical from the 2-methyl-1-napthyl ion was reported which is in keeping with the resulting

ion not having the potential to stabilize the positive charge which would develop.

The peak at m/e 141 in fig. 7.3, provides evidence that dehydration occurs from the 7-methyl-8-hydroxyquinolyl ion and this is shown in eq. 7.10.

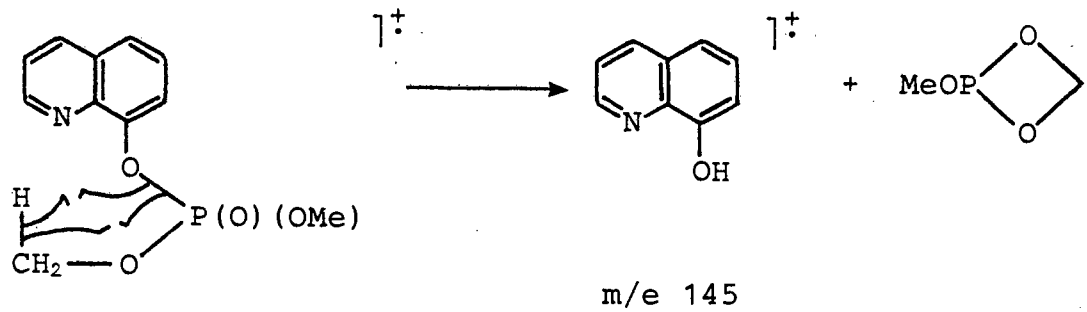


(7.10)

m/e 141

This fragmentation is an example of the "ortho effect" and is typical of o-methylphenols.[115] A $(M - 18)^{+\cdot}$ peak has also been reported for the 2-methyl-1-napthol ion.[114]

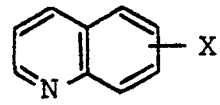
The intense peak at m/e 145 (relative intensity 40%) results from hydrogen migration and loss of methylmethylene phosphite[112] from the molecular ion of dimethyl-(quinolin-8-yl) phosphate to give the molecular ion of 8-hydroxyquinoline. This is illustrated in eq. 7.11.



(7.11)

m/e 145

Pathway *d* in scheme 7.2 shows the important fragmentations of 8-hydroxyquinoline. One major fragmentation process involves the facile loss of neutral CO from the phenolic ring and this is probably promoted by the neighbouring nitrogen atom providing a basic centre which can accept the proton from the hydroxyl function. This is followed by decomposition of the pyridine ring resulting in expulsion of HCN and formation of the $C_7H_5^{+\cdot}$ radical ion at m/e 89. This is a characteristic property of compounds of type 7.4.[116]

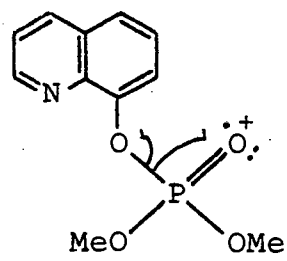


X = OR, SR, NH_2

7.4

Further fragmentation of the $C_7H_5^{+\cdot}$ species with loss of ethyl radical gives rise to a peak at m/e 63 assigned to the $C_5H_3^{+}$ ion.

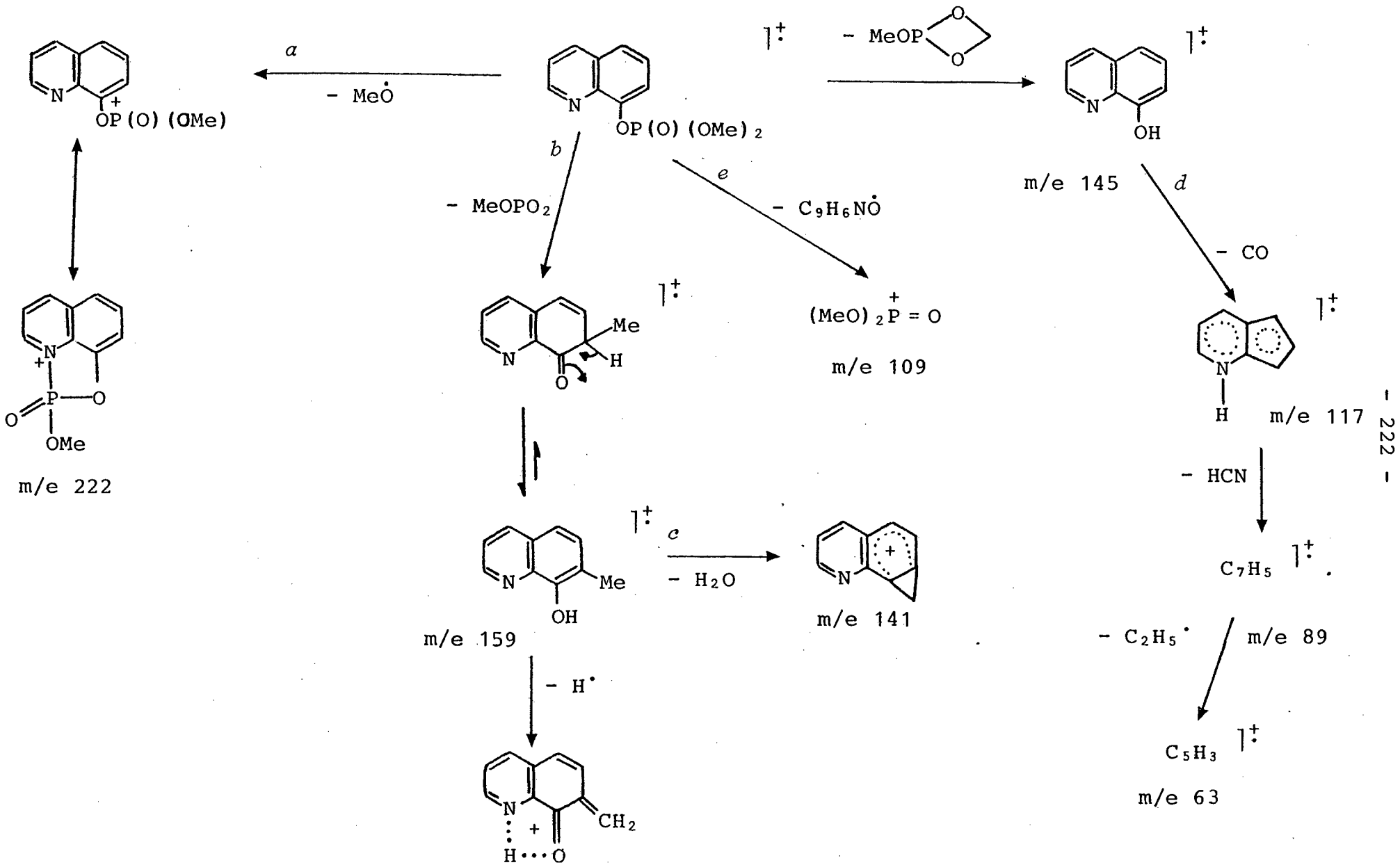
One final fragmentation of interest is that which gives the fragment at m/e 109. This peak was observed in the mass spectrum of A and is due to the dimethylphosphorylium ion. It is generated by simple homolytic bond cleavage and expulsion of the $C_9H_6NO^{\cdot}$ radical, as shown in eq. 7.12 (scheme 7.3, pathway *e*).



$$\longrightarrow \quad (MeO)_2\overset{+}{P}=O \quad + \quad C_9H_6NO^{\cdot} \qquad (7.12)$$

m/e 109

Scheme 7.2

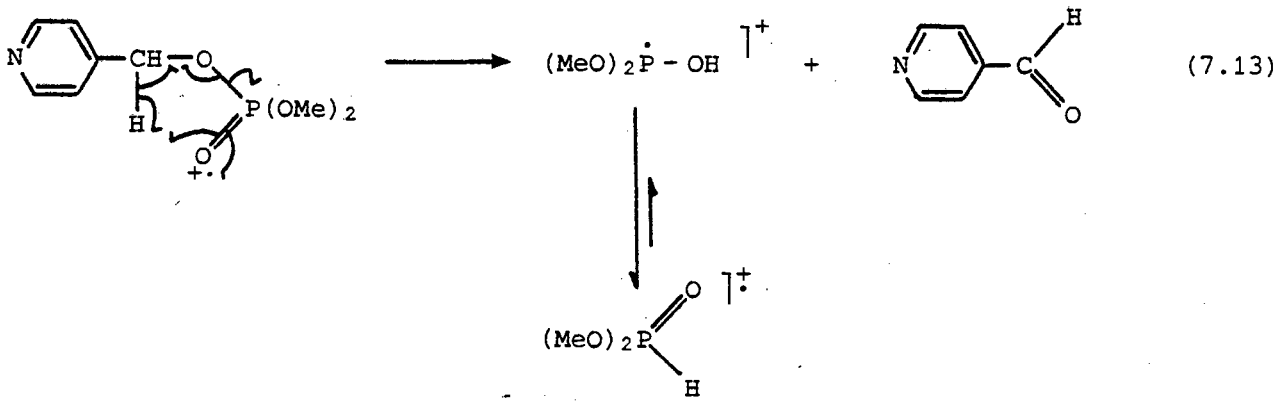

a
- MeO·
OP(O)(OMe)
m/e 222
OP(O)(OMe)2
b
- MeOPO2
e
- C9H6NO·
(MeO)2P=O
m/e 109
- MeOP
m/e 145
d
- CO
m/e 117
- HCN
C7H5
- C2H5·
m/e 89
C5H3
m/e 63
m/e 159
- H·
c
- H2O
m/e 141
- 222 -

7.5 FRAGMENTATION BEHAVIOUR OF DIMETHYL-(4-PYRIDYLMETHYL) PHOSPHATE, D.

The important ions formed from the parent-molecule ion are listed in table 7.4. The proposed fragmentations are shown in scheme 7.3.

One of the four compounds synthesized, dimethyl-(4-pyridylmethyl) phosphate contains the nitrogen heteroatom the furthest removed from the reactive centres and it is therefore expected to have the least influence, if any, on the electron impact-induced fragmentation patterns of the phosphate function. Not surprising, the molecular ion of this compound, m/e 217, is the most stable of the four compounds under study, having a relative intensity of 83% of the base peak (fig. 7.4).

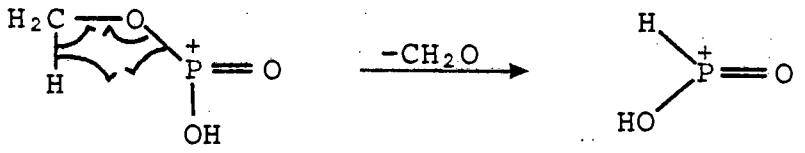
The most abundant fragment ion (m/e 110) is due to the dimethyl phosphite molecular ion resulting from expulsion of a neutral molecule of 4-pyridyl carboxaldehyde from the parent-molecule ion, probably via a 5-membered transition state as shown in eq. 7.13.



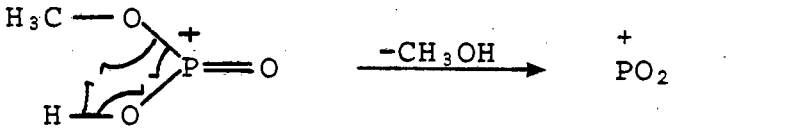
(7.13)

m/e 110

Besides the few fragmentations discussed in a following paragraph, the major fragmentations in the spectrum are those of the dimethyl phosphite ion.[117] Loss of a hydrogen atom from the base peak is a reasonably favourable process yielding m/e 109 (relative intensity 39%). This path then leads to the formation of a peak, m/e 79, by expulsion of formaldehyde. Formaldehyde is also lost quite readily from the base peak giving m/e 80, which in turn, expels methyl radical to give the fragment ion at m/e 65. The peak m/e 95 arises by cleavage of a O-CH_3 bond and elision of a mass 15 moiety, $\dot{C}H_3$. Subsequent loss of formaldehyde occurs probably by way of a 4-membered transition state as shown in eq. 7.14a. Another fragmentation mode of m/e 95, also via way of a 4-membered transition state, is hydrogen migration with expulsion of methanol to give $\overset{+}{P}O_2$ at m/e 63 (eq. 7.14b).



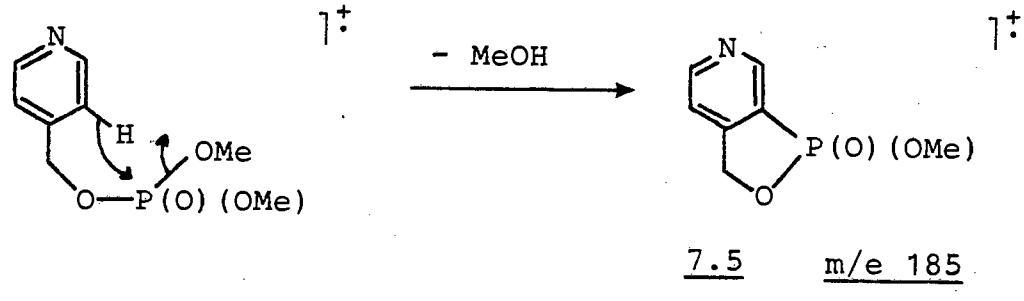
m/e 95 m/e 65 (7.14a)



m/e 95 m/e 63 (7.14b)

The fragment ions at m/e 202 and 185 are minor, relative intensity 1.5 and 3% respectively, but are of importance in view of the fact that they are in accordance with fragmentations observed for substrate A. It is important to note in the mass spectrum of substrate D, the complete absence of a peak (m/e 186) resulting from the loss of methoxy radical from the molecular ion. This behaviour

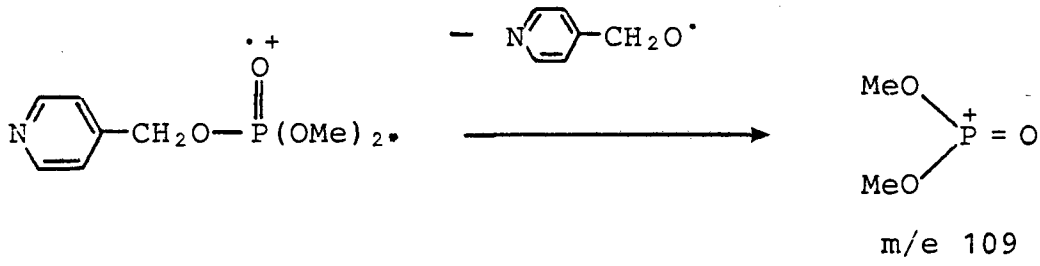
of the 4-pyridylmethyl ester contrasts sharply with that of its 2-pyridylmethyl isomer, for which the (M - 31) peak was formed with *ca.* 20% relative abundance. This difference can be taken as a measure of the importance of the resonance stabilization of the phosphorylium ion formed (see eq. 7.1), possible for the 2-isomer, but not available for system D. Instead of loss of MeO$^{\bullet}$, the mass spectrum of D shows that a methanol molecule can be lost from the molecular ion, yielding the low intensity peak (relative abundance 3%) of m/e 185. This fragmentation requires abstraction of a hydrogen atom by the methoxy group; this abstraction takes place most likely from position 3(5) of the pyridine ring (eq. 7.15) yielding an oxaphosphole-1-oxide system (7.5), a pyridine analogue of a known benzo derivative.[118]



(7.15)

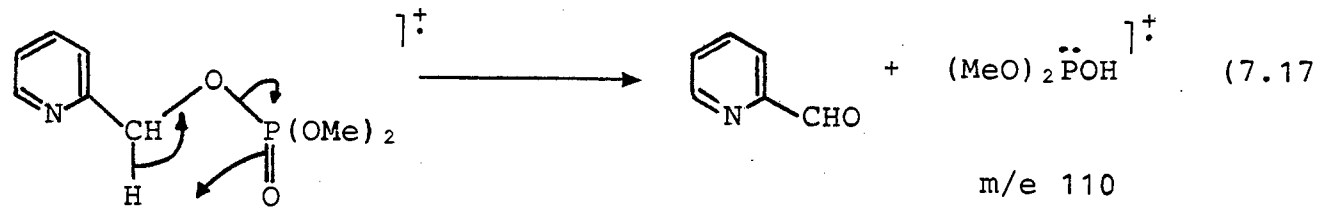
7.5 m/e 185

In common with substrate A, the mass spectrum of D contains a peak at m/e 109 which is assigned to the dimethylphosphorylium ion. As mentioned earlier, this ion can be produced *via* the hydrogen abstraction from the molecular ion of dimethyl phosphite, the additional pathway available is the direct P-O bond cleavage in the molecular ion of D, as shown below.



m/e 109 (7.16)

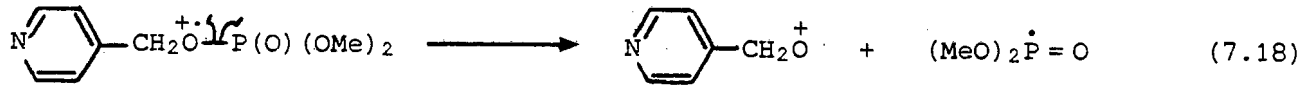
Pertinent with the comparison of the major fragmentation pathway from the molecular ion of D (eq. 7.13) is a consideration of the analogous fragmentation from compound A. Equation 7.17 shows the analogous hydrogen rearrangement which results in formation of the dimethyl phosphite radical ion species at m/e 110.



m/e 110 (7.17)

However, examination of the mass spectrum of dimethyl-(2-pyridylmethyl) phosphate (fig. 7.1) has shown that the most important fragmentation from the molecular ion is expulsion of the dimethylphosphoranyl, radical and formation of the base peak at m/e 108 (see eq. 7.2). In fact contribution from the above pathway (eq. 7.17) to the fragmentation from the molecular ion can be ignored as m/e 110 is negligible. The fundamental difference between eq. 7.17 and eq. 7.2 lies in the nature of the hydrogen ion acceptor - oxygen or nitrogen respectively. Absence of a peak at m/e 110 of any significance in the mass spectrum of compound A is therefore explained by the low basicity of the phosphoryl oxygen atom compared to nitrogen, thus making the latter a more favourable hydrogen acceptor. In this respect therefore, due to geometry reasons,

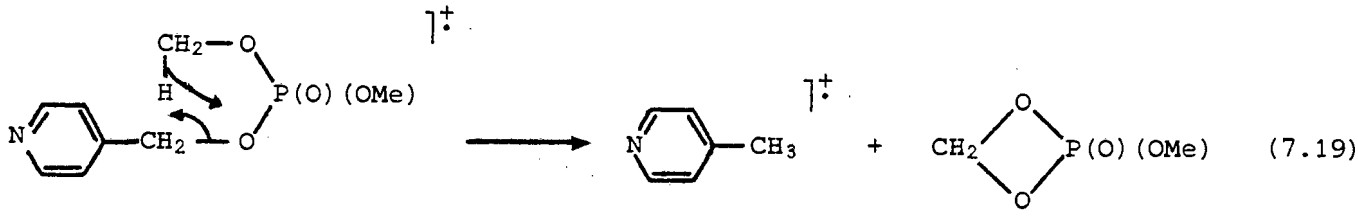
one can quite reasonably accept that the phosphoryl oxygen in compound D, has no competition from the pyridyl nitrogen. However, a peak at m/e 108 (relative intensity 83%) is observed in the mass spectrum of compound D and is assigned to the $C_5H_4NCH_2O^+$ species which we propose arising as a result of simple homolytic cleavage of the P-OCH_2Py bond with expulsion of a dimethylphosphoryl radical (eq. 7.18).



(7.18)

m/e 108

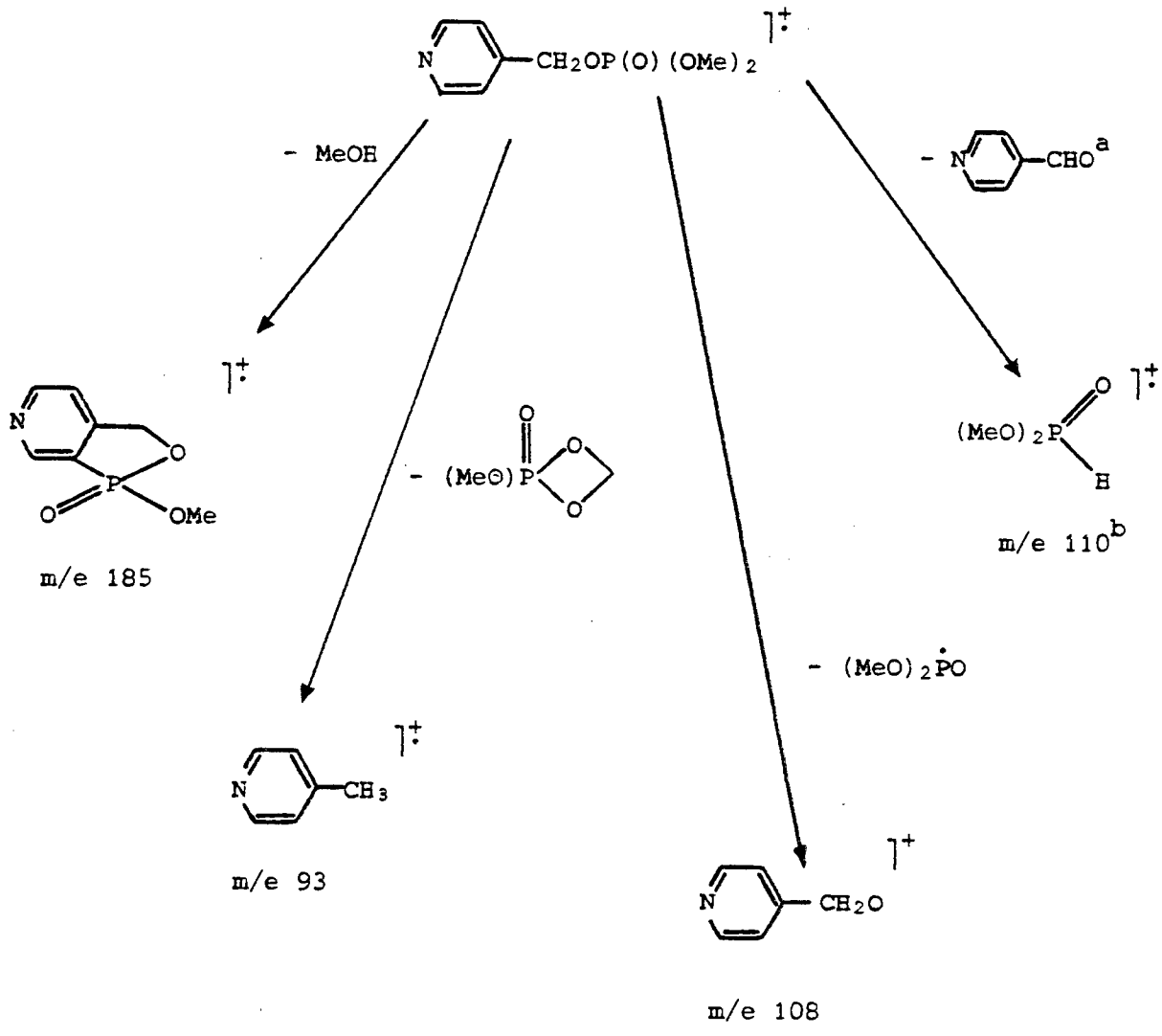
The fragment ion at m/e 93 (relative intensity 56%) is assigned to the radical ion of 4-picoline. It probably results from hydrogen rearrangement accompanied by expulsion of methylmethylene phosphate as shown in eq. 7.19.



(7.19)

m/e 93

Scheme 7.3 Fragmentation Pathways for dimethyl-(4-pyridyl-methyl) phosphate, D.



[a]Major fragmentation

[b]Reference 117

CONCLUSION

Characterization of this class of compounds by mass spectrometry proved interesting and besides the often complex behaviour of the phosphate group and the ester substituents, it showed that the nitrogen heteroatom, particularly in A and B, played more than just a 'spectator role' in some of the electron induced fragmentations. (Many of the bond-forming reactions involved the nitrogen lone-pair electrons.) Fairly intense molecular ions were observed for substrates A, C and D which is typical for organophosphorus esters.[119] The low relative intensity of the molecular ion of the ethyl derivative B is attributed to the very favourable elimination reaction following the McLafferty rearrangement. In addition, many of the most important fragmentations involved hydrogen atom rearrangements.

Table 7.1 Main Ions in the Mass Spectrum of Dimethyl-(2-pyridylmethyl) phosphate, A.

m/e	Relative Abundance %
217 (molecular ion)	36
202	3.2
186	20
109	22
108	100
93	17
80	7
79	12

Table 7.2 Main Ions in the Mass Spectrum of Dimethyl-[β-(2-pyridylethyl)] phosphate, B.

m/e	Relative Abundance %
231 (molecular ion)	4
122	15
109	36
106	64
105	100
79	76

Table 7.3 Main Ions in the Mass Spectrum of Dimethyl-(quinolin-8-yl) phosphate, C.

m/e	Relative Abundance %
253 (molecular ion)	54
222	22
159	23
158	100
145	40
141	9
117	14
109	11
89	13
63	10

Table 7.4 Main Ions in the Mass Spectrum of Dimethyl-(4-pyridylmethyl) phosphate, D.

m/e	Relative Abundance %
217 (molecular ion)	83
202	1.4
185	3
110	100
109	39
108	83
95	45
93	56
80	26
79	22
65	45
63	16

Figure 7.1 Mass spectrum of dimethyl-(2-pyridylmethyl) phosphate, A

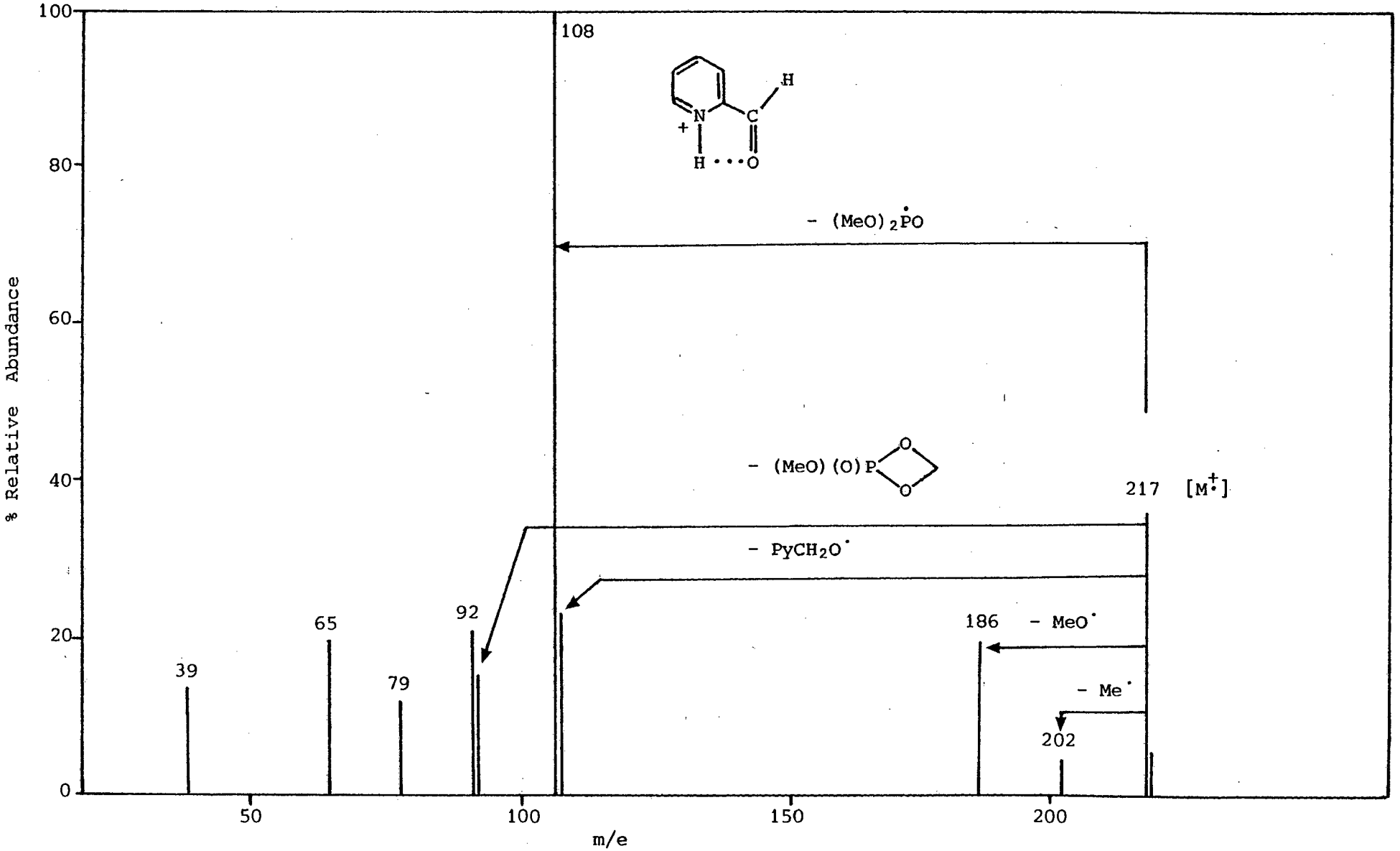


Figure 7.2 Mass spectrum of dimethyl-[β-(2-pyridylethyl)] phosphate, B

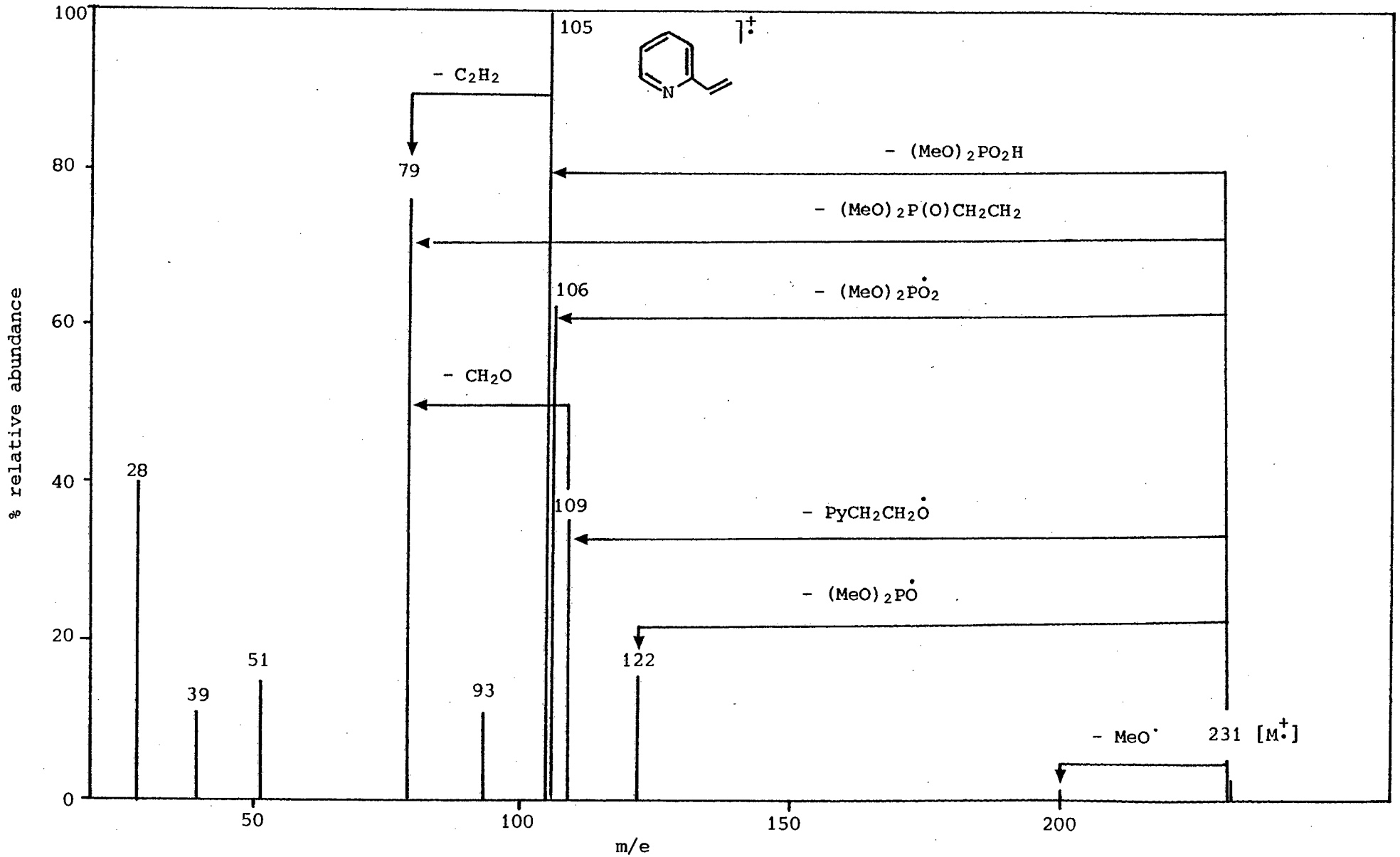


Figure 7.3 Mass spectrum of dimethyl-(quinolin-8-yl)phosphate, C

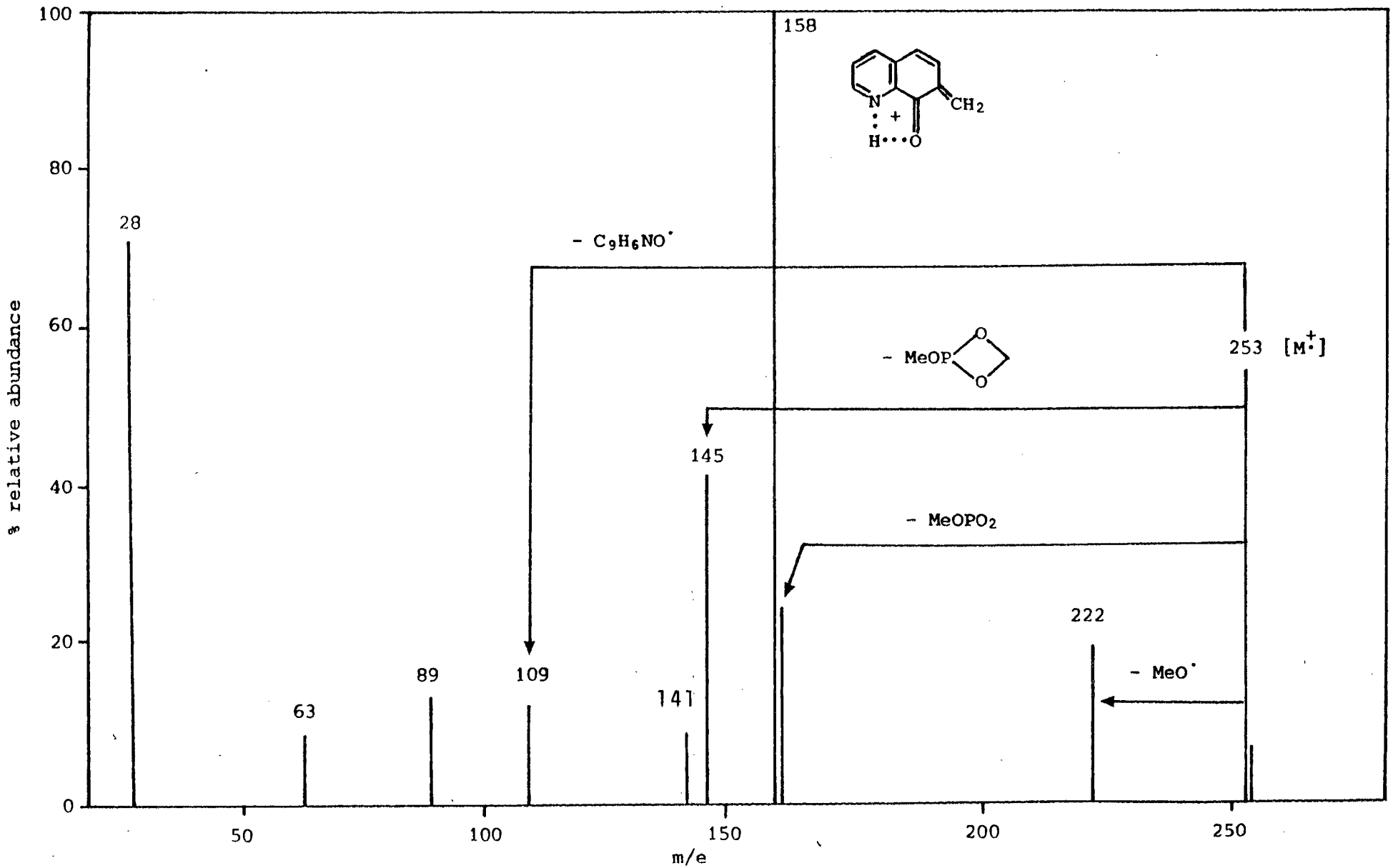
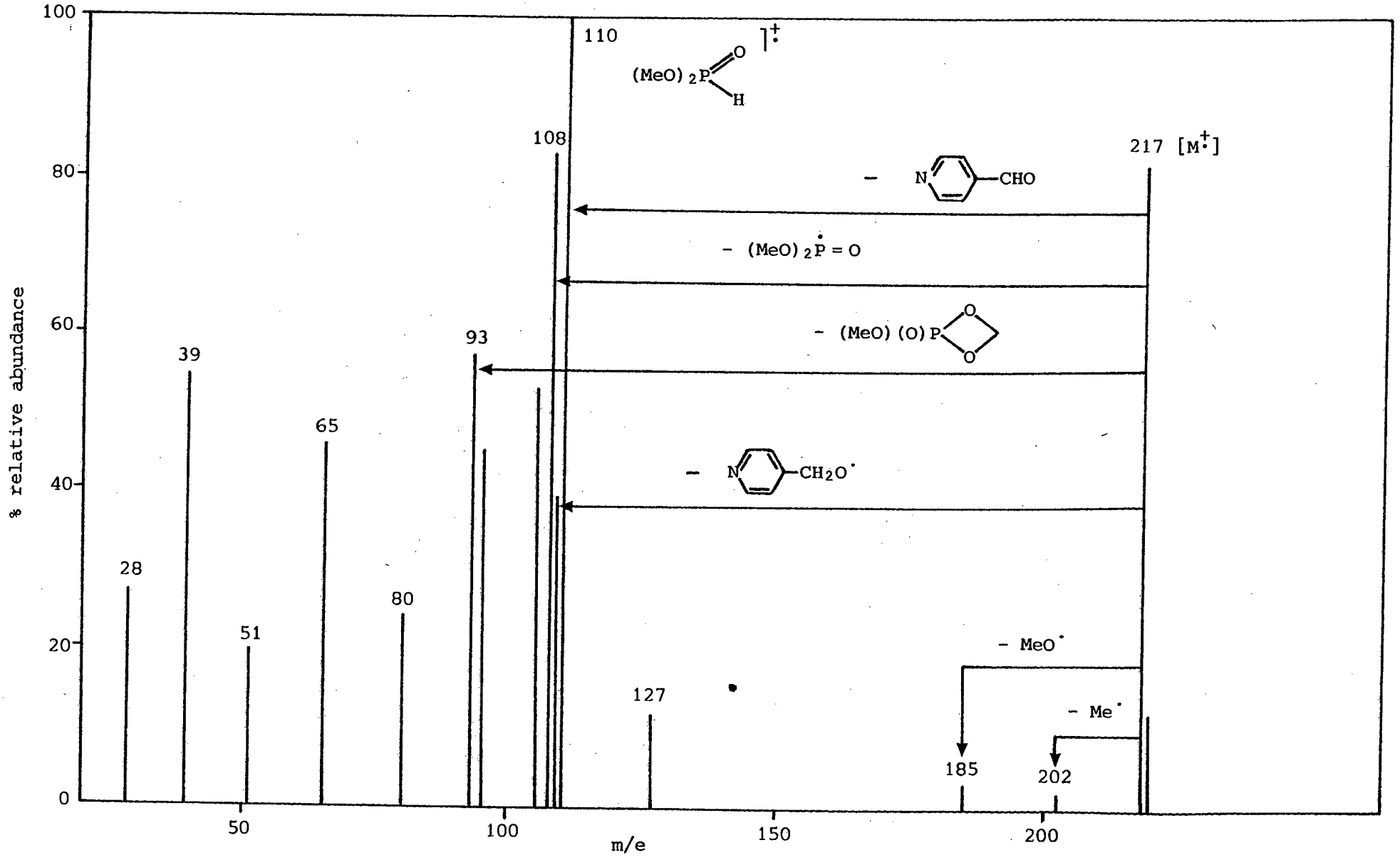


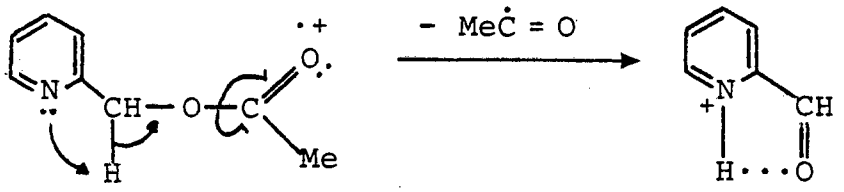
Figure 7.4 Mass spectrum of dimethyl-(4-pyridylmethyl) phosphate, D



7.6 FRAGMENTATION BEHAVIOUR OF 2-PYRIDYLMETHYL ACETATE, [β-(2-PYRIDYL)ETHYL] ACETATE AND 8-QUINOLYL ACETATE.

7.6.1 2-PYRIDYLMETHYL ACETATE, E

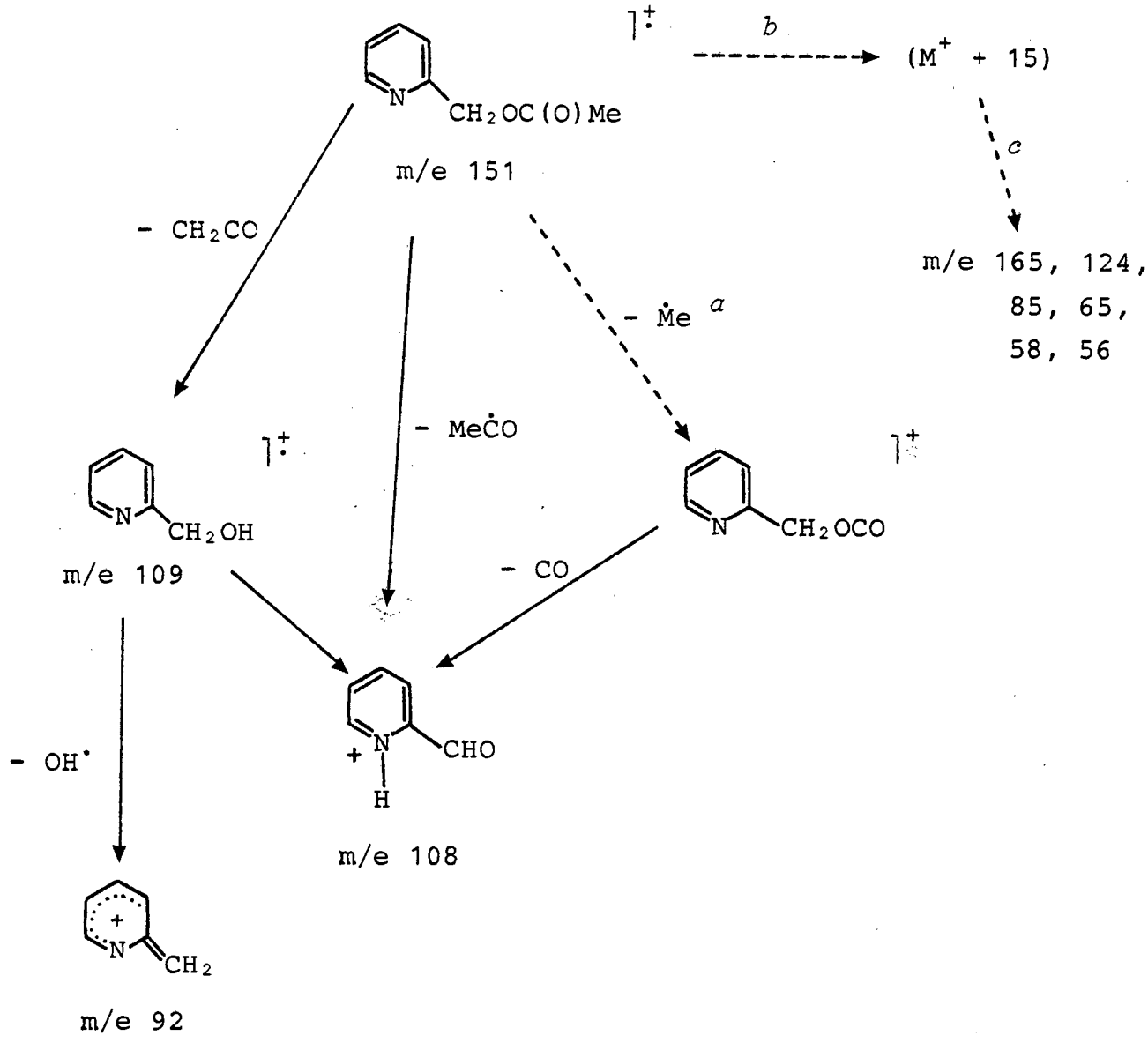
The parent-molecular ion was observed but never dominated the spectra (see fig. 7.5a and 7.5b and table 7.4). The base peak varied under different conditions, appearing at m/e 39 or 42 ($C_3H_3^+$ or $CH_2=CO]^{+\cdot}$ respectively) at 70 ev and 200°C or at m/e 108 under conditions of low temperature (~80°C) and low electron voltage (12.5 eV). This last peak is assigned to protonated 2-pyridylmethanal. This is postulated as forming in a manner analogous to that observed for dimethyl-(2-pyridylmethyl) phosphate (see eq. 7.2).



(7.20)

The mass spectrum of substrate E is complicated by the appearance of a ($M^+ + 15$) fragment ion at m/e 166. Despite the purity of the substrate as indicated by elemental analysis and ^1H NMR spectroscopy, this peak is always present in the mass spectrum, even under conditions of relatively low source temperature (~80°C) and low beam energy (12.5 eV). A number of peaks (m/e 165, 148, 124, 85, 67, 58, 56 and 39) are postulated as being daughter fragment ions arising from m/e 166 as no other reasonable explanation can be offered for their existence. The fragmentations most likely to occur in E are shown in scheme 7.4.

Scheme 7.4



[a] M^+ - Me not observed

[b] No plausible explanation is offered for $M^+ + 15$ peak

[c] Daughter fragment ions of m/e 166

7.6.2 [β-(2-PYRIDYLETHYL)] ACETATE, F.

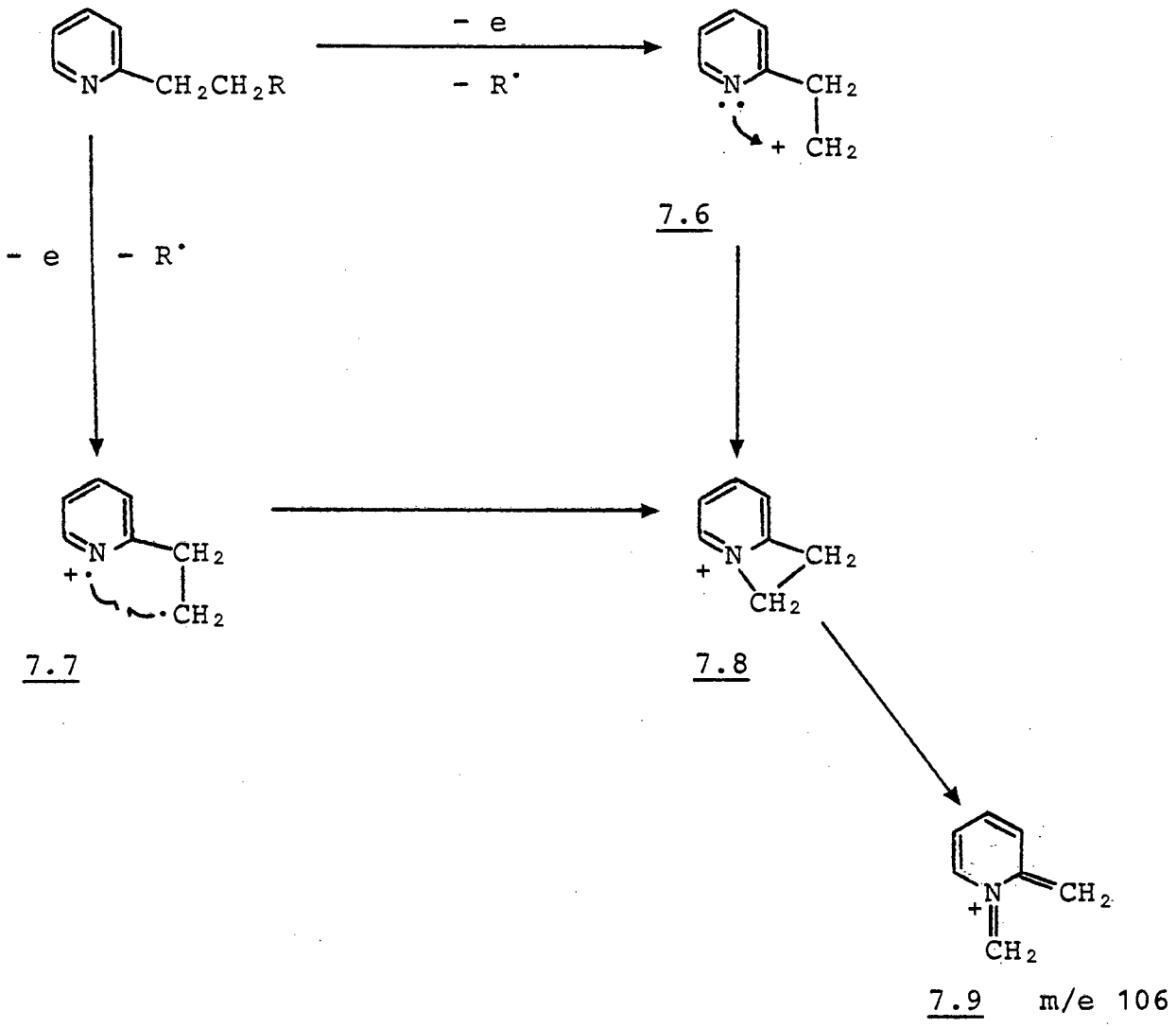
The mass spectrum of [β-(2-pyridylethyl)] acetate appears less complicated than that of its methyl analogue (see fig. 7.6). The molecular ion is very weak with a relative abundance of less than 2% of the base peak. As seen from table 7.4, ketene elimination from the parent molecular ion is not a favourable reaction pathway. Instead γ and δ bond cleavage* and the McLafferty rearrangement become the prevalent pathways for fragmentation.

In the first case, loss of acetoxy radical can give two species, 7.6 and 7.7 (scheme 7.5) with the positive charge residing on carbon and nitrogen respectively. To account for the favourable γ-cleavage in 2-substituted pyridines, Spiteller[120] invoked stabilization of the alkyl carbonium site in 7.6 by the electron pair on nitrogen, followed by rearrangement of the resulting 4-membered ring in 7.8 to give 7.9 (scheme 7.5). The reaction can, of course, also be formulated through the species 7.7.

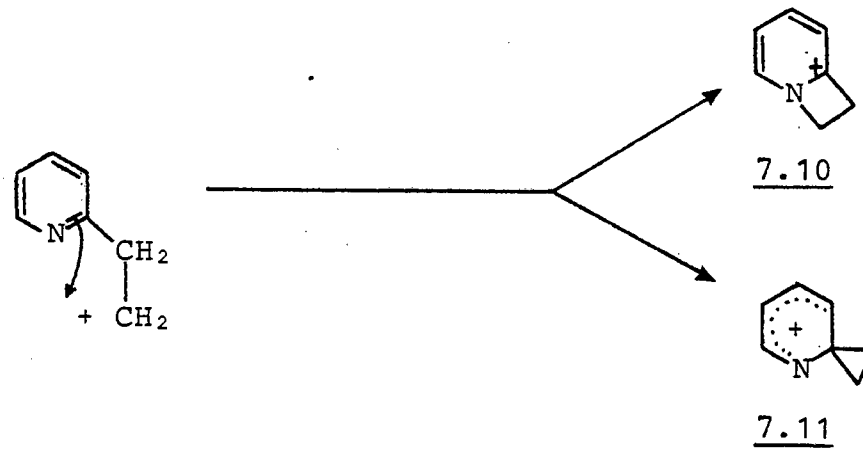
The carbonium ion in 7.6 can be stabilized by the π electrons of the heteroaromatic ring as shown in eq. 7.21. This can be considered as a form of anchimeric assistance observed in the gas phase. Chapter 9 describes a detailed investigation of anchimeric assistance by a phenyl group in β-arylethyl phosphate derivatives.

*Nomenclature for bond cleavage is standard i.e. for 2-substituted pyridines - $Py \overset{\alpha}{-} CH_2 \overset{\beta}{-} CH_2 \overset{\gamma}{-} O \overset{\delta}{-} X$ where Py = C_5H_4N.

Scheme 7.5



R = OC(O)Me



7.10

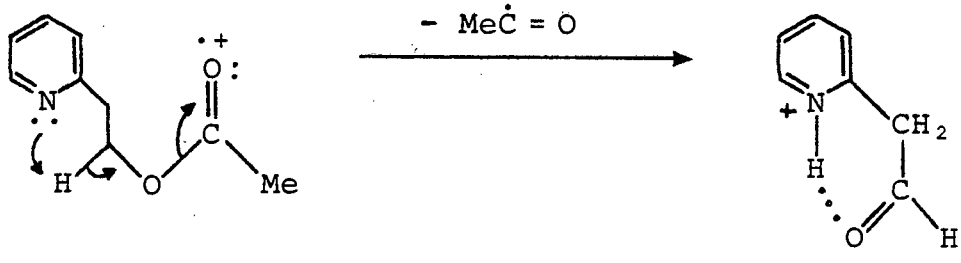
7.11

spirotype ion

(7.21)

Cooks and co-workers[121] have suggested that γ cleavage mechanisms in 2-alkylpyridines which involve cyclization by nitrogen to give ions of type 7.10 are not observed. Rather, they believe that formation of a spiro phenonium type ion, 7.11, is probably involved in the alkylpyridine fragmentations. On these grounds we postulate the peak at m/e 106 as being due to 7.11 in eq. 7.21.

In a different domain, δ bond cleavage can be considered in conjunction with proton transfer. For example, abstraction of a β-hydrogen by the pyridyl nitrogen atom, and O-C bond cleavage, with expulsion of the $C(O)CH_3$ radical gives rise to the base peak at m/e 122. It is possible that this peak - protonated 2-pyridylethanal is stabilized by hydrogen bonding as shown in eq. 7.22

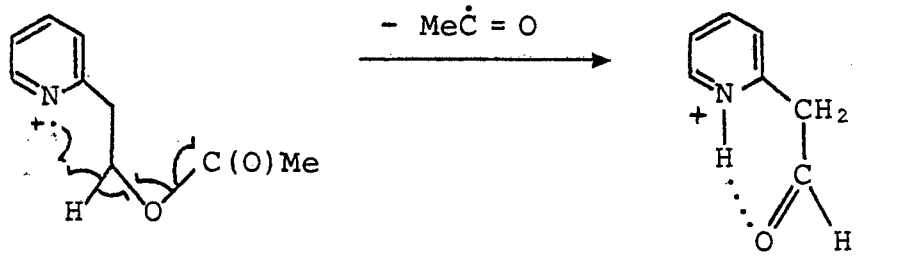


m/e 165

m/e 122 (base peak)

(7.22)

Although this type of fragmentation has already been observed for dimethyl-[β-(2-pyridylethyl)] phosphate, it was of less importance and gave rise to a signal of relative abundance of only 15% of the base peak. It must be noted that in illustrating the formation of the base peak by eq. 7.22, a carbonyl oxygen lone-pair electron has been considered ionized in the initial electron impact. However, involvement of the molecular ion in which a nitrogen lone-pair electron has been removed can also be considered as the parent ion for the m/e 122 fragment. This is shown in eq. 7.23.

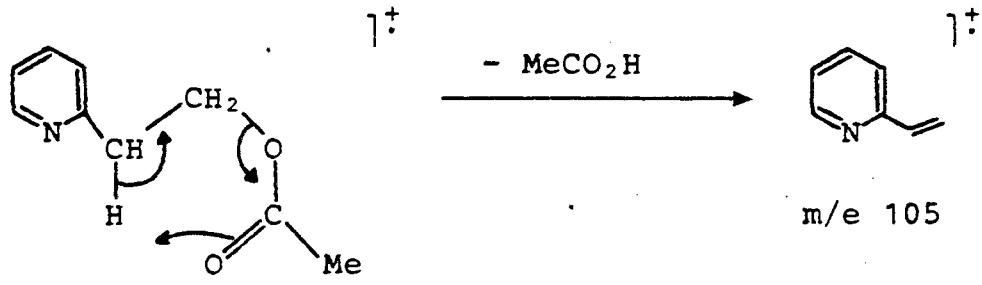


(7.23)

m/e 122 (base peak)

Cooks[121] has stated that the major bond forming reactions in a series of 2-substituted pyridine derivatives appears to involve a form of the molecular ion in which a nitrogen lone-pair electron has been removed on ionization which lends support for eq. 7.23 compared to eq. 7.22.

The McLafferty rearrangement involving loss of acetic acid gives rise to the peak at m/e 105. Whereas this fragmentation is responsible for the formation of the base peak in the phosphate derivative, it accounts for a peak of relative intensity only 20% in the present case.



(7.24)

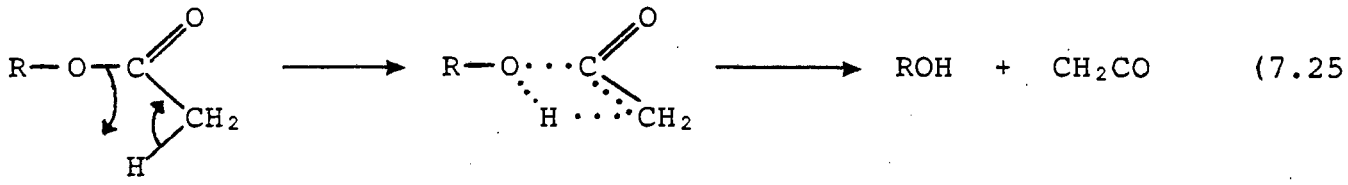
It would be interesting to know whether this greater susceptibility of phosphate esters to elimination observed in mass spectroscopy is paralleled under different (e.g. pyrolysis) conditions. Unfortunately, to our knowledge there is no data available on thermolysis of substituted ethyl phosphoric esters.

7.6.3 8-QUINOLYL ACETATE, G.

The mass spectrum of 8-quinolyl acetate is relatively simple (fig. 7.7). No parent-molecular ion was observed and the base peak at m/e 145 has the elemental composition of 8-hydroxyquinoline. The spectrum below m/e 145 is qualitatively identical to that of 8-hydroxyquinoline with the ejection of carbon monoxide as the first fragmentation, followed by the loss of HCN to give m/e 89.

7.6.4 CONCLUSION

One general feature in the mass spectra of the three acetates is the loss of ketene from the parent-molecular ion giving an M - 42 species. Ketene elimination can be considered as proceeding way of a 4-membered cyclic transition state as shown in eq. 7.25.



(7.25)

We expect heteroaromatics to behave similarly to phenolic acetates in losing the elements of ketene, rather than those of acetic acid which is characteristic of their alcoholic counterparts.[122] The abundance of the ion formed by ketene elimination is given in table 7.5 and can be compared to the loss of acetic acid - an M^+ - 60 fragmentation. These results are in accord with the results of Cooks and co-workers who studied the sequence $M^{+\cdot}$ - AcOH - $H^{\cdot}$ for 2-, 3- and 4-substituted pyridyl acetates.* For both the 3- and 4-pyridyl acetates, the authors found that this sequence could account for the base peak in the mass spectra, but an ion of only 9% abundance was observed in the 2-pyridyl compound.

*The propylpyridyl acetates were investigated.

Table 7.4 Main Ions in the Mass Spectra of (2-pyridylmethyl) acetate, [β-(2-pyridylethyl)] acetate and 8-hydroxyquinolyl acetate.

	Substrate		
	E[a]	F[b]	G[a]
M.W.	151	165	187
m/e	Relative Intensity %		
Molecular ion	30 (2)	<2	-
M + 1	-	4	-
M + 15	68 (22)		
39	100	17	9
43	-	92[c]	13
79	11	19	-
89			15
92	12	9	-
93	5	55	-
105	4	19	-
106	3	50	-
108	55 (100)	-	-
109	55 (82)	-	-
117	-	-	36
122	-	100	-
123	-	8	-
145	-	-	100

[a]Beam energy 70 eV, source temperature, *ca.* 200°C. Figure in parenthesis obtained at *ca.* 12.5 eV and 80°C.

[b]Beam energy *ca.* 35 eV, source temperature, *ca.* 45°C.

[c]m/e 43 not consistently present.

Table 7.5 Comparison of selected ions in the mass spectra of E, F and G.

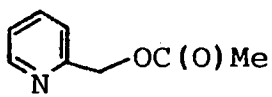
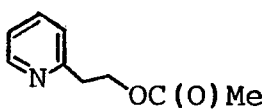
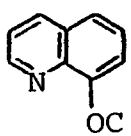
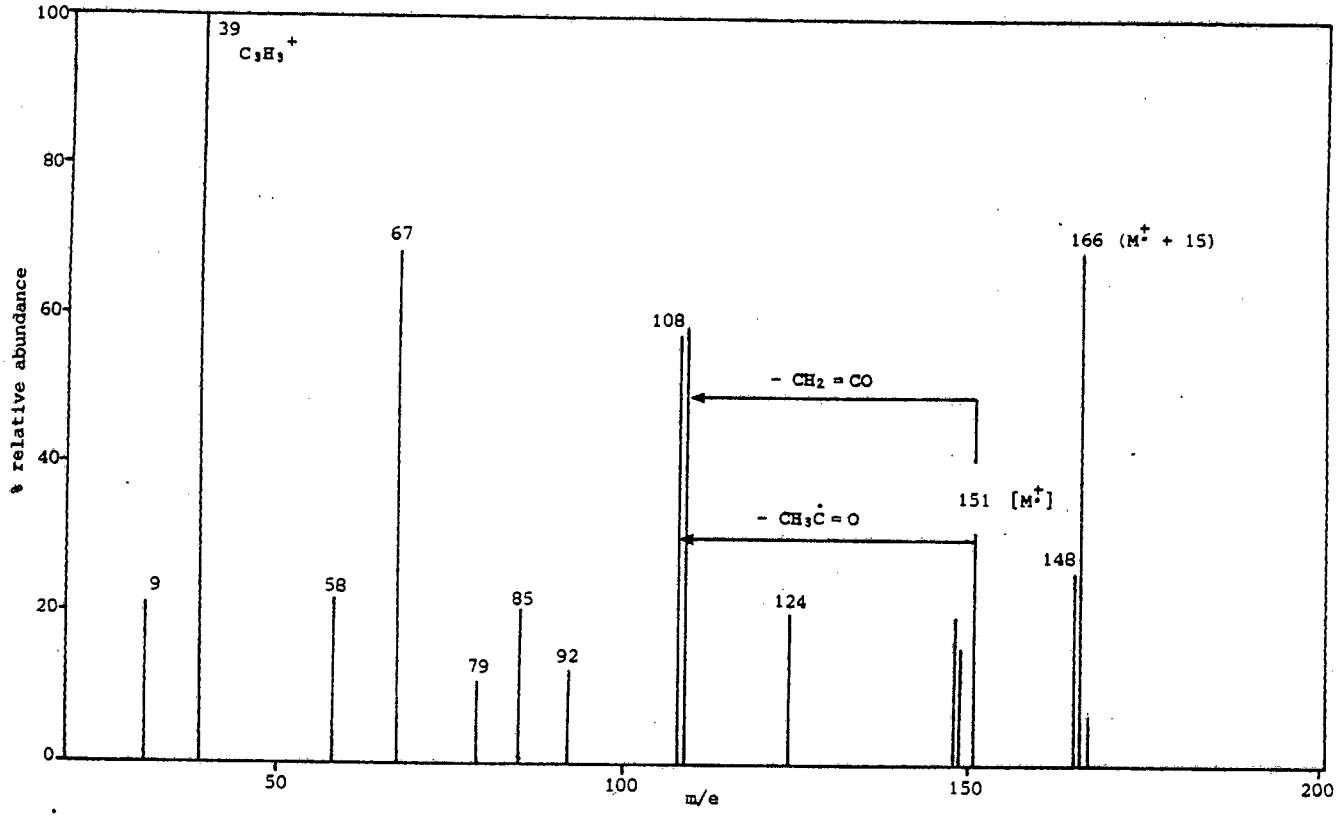
	Beam Energy	Source Temp.	M^+ m/e	M^+ %	$M^+ - 42$	$M^+ - 60$	Base Peak
	12.5 eV	80°C	151	2%	82%	4%	m/e 39
	70 eV	200°C		30%	55%	-	m/e 108
	35 eV	45°C	165	<2%	-	20%	m/e 122
	70 eV	200°C	187	-	100%	-	m/e 145

Figure 7.5 Fragmentation pattern dependence of 2-pyridylmethyl acetate upon the electron beam energy and ion source temperature.

(A) 70 eV 200°C



(B) 12.5 eV 80°C

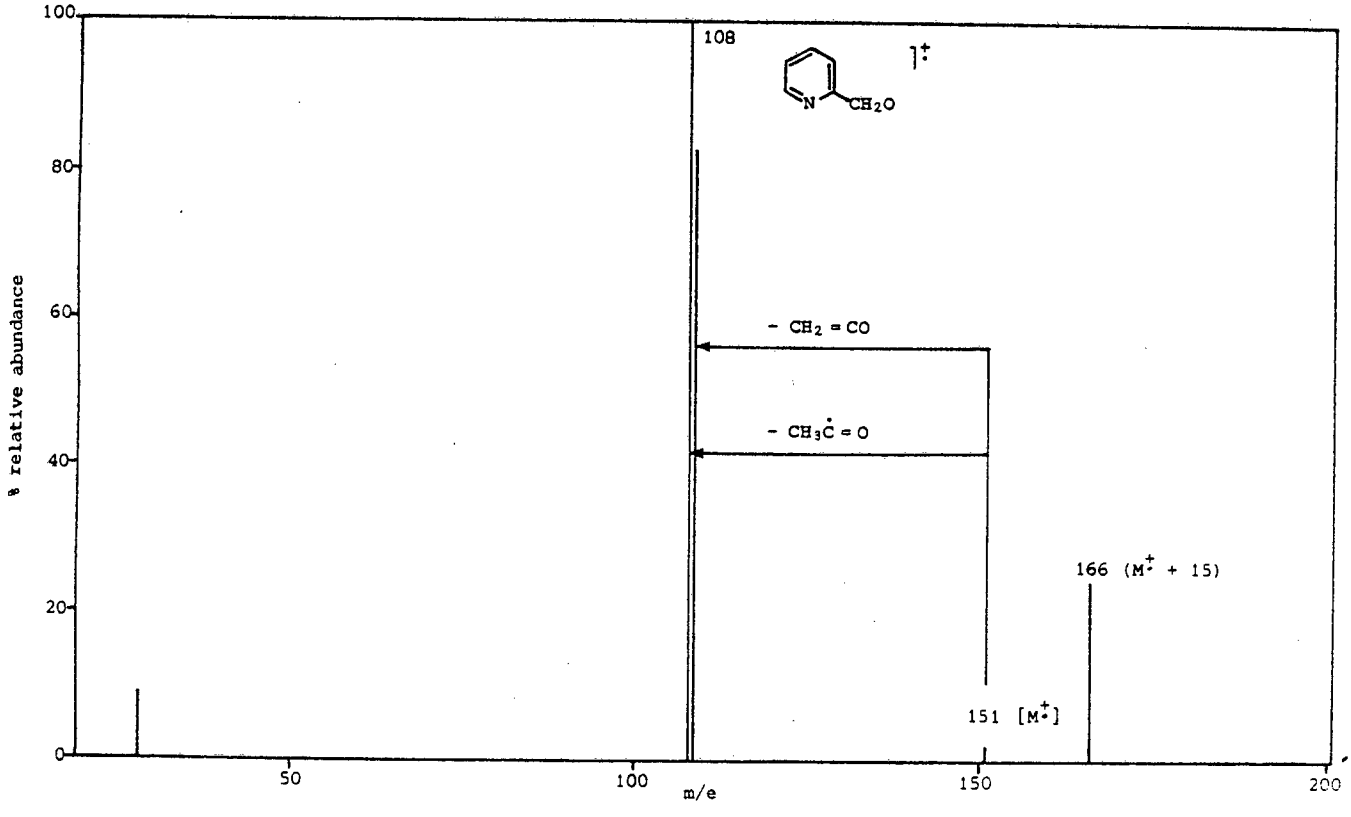


Figure 7.6 Mass spectrum of [β-(2-pyridylethyl)] acetate, E

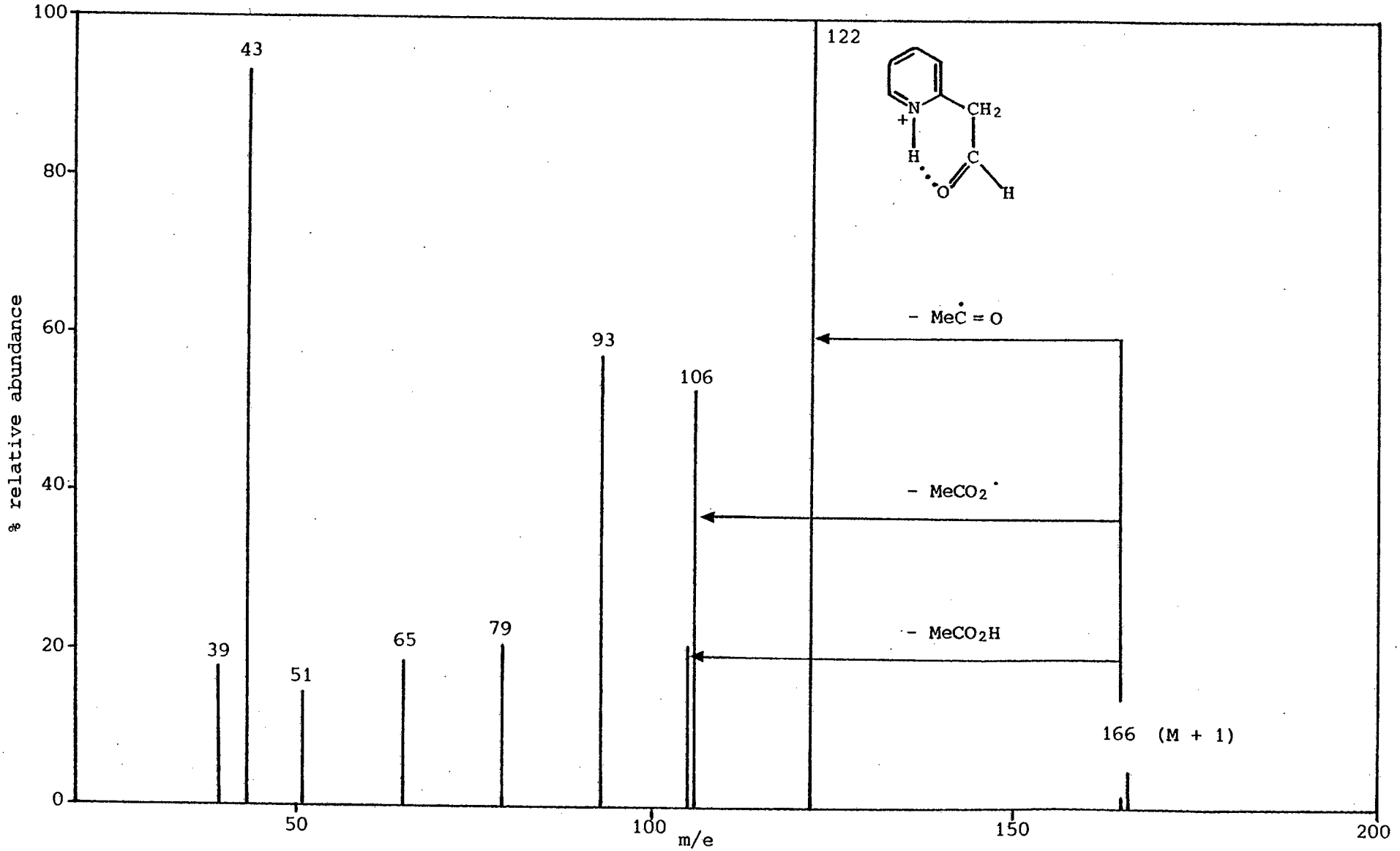
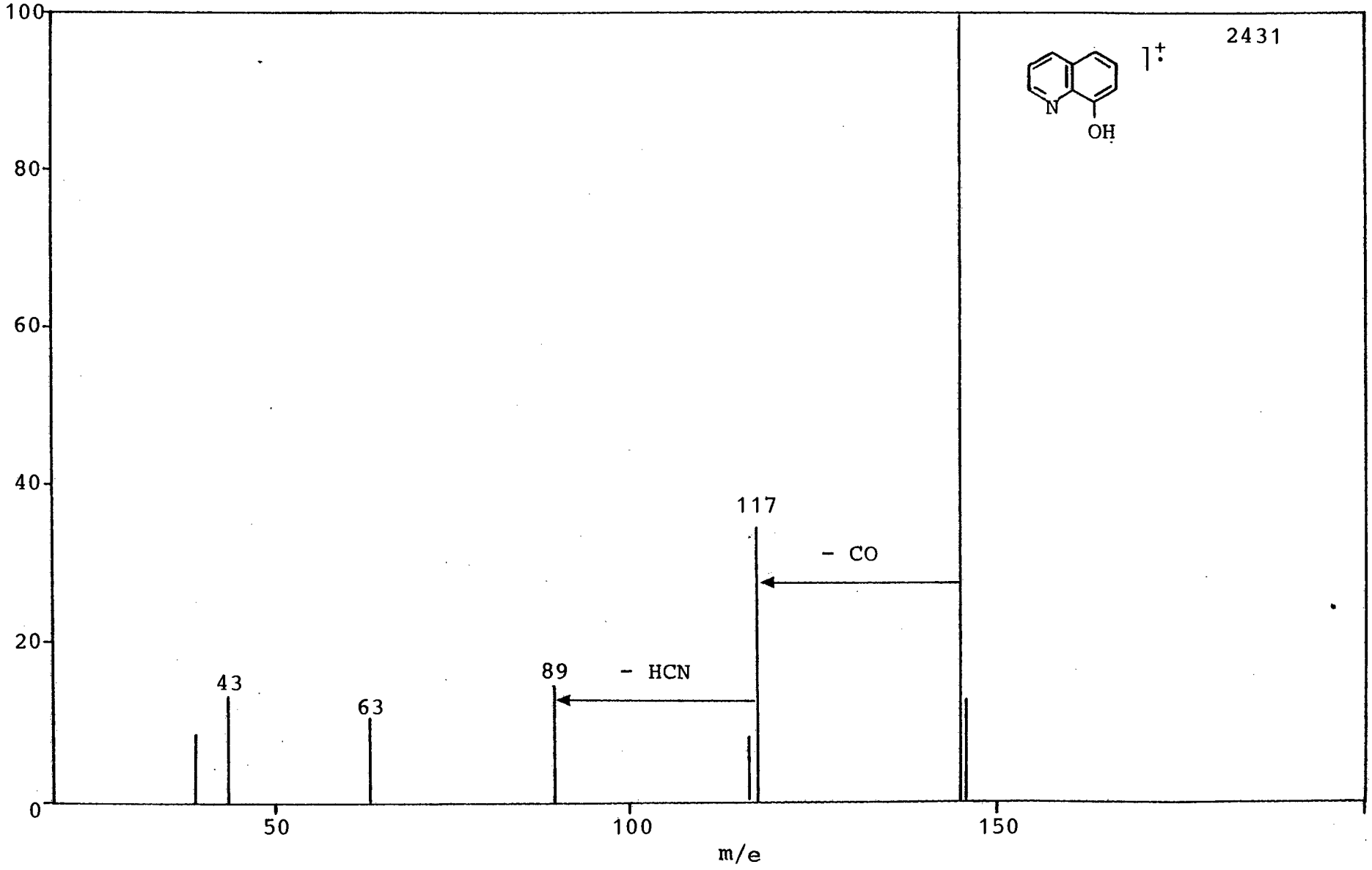


Figure 7.7 Mass spectrum of 8-quinolyl acetate, G



Chapter 8

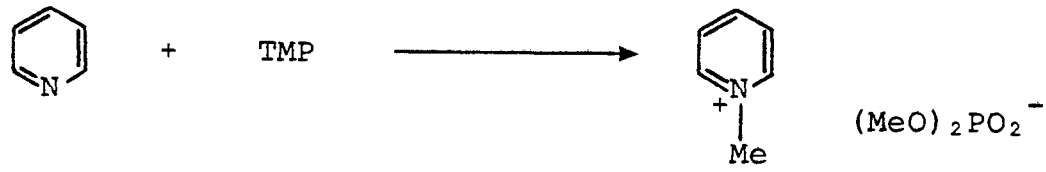
Methyl Group Transfer from Trimethyl Phosphate to Pyridyl Nitrogen

8.1 INTRODUCTION

Our experiments related to ch.s 4 and 5 have revealed a pronounced solvent effect on the rates of alkylation of the nitrogen atom of substrates A - D by an alkyl phosphate function and we have observed that these substrates are converted into their N-methyl derivatives in aqueous solution much faster than in any other solvent, even of high polarity. Since the alkylation of a nitrogen atom by an alkyl phosphate function is synthetically important and relevant to the mutagenic and carcinogenic activity of alkylating agents,[4] and also because water is the medium for all reactions proceeding *in vivo*, we were encouraged to investigate in more detail, the effect of water on the alkylating behaviour of an organic phosphate.

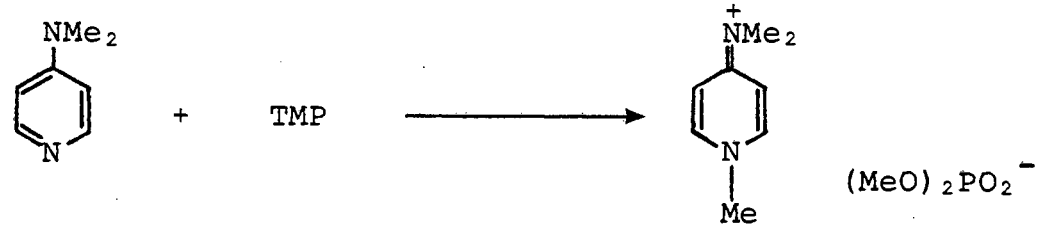
Our objective was to examine methyl group transfer from trimethyl phosphate (TMP) to two simple model compounds containing nitrogen acceptor centres (eq.s 8.1 and 8.2). The study was directed at determining the effect of medium composition on the methyl transfer reaction (pure solvents and mixed solvents were investigated) and in addition, to obtaining activation parameters for the reactions in pure solvents.

Pyridine and 4-(dimethylamino)-pyridine (4DMAP) were selected as the two model nitrogen-containing heterocyclic compounds. The latter compound was chosen because of the greater availability of the unshared electron pair of the nitrogen which would subsequently lead to a faster reaction.[123]



(8.1)

8.1

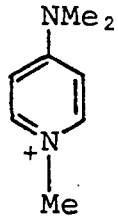


(8.2)

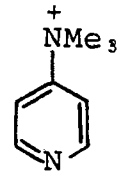
8.2

8.2 RESULTS

One of the fundamental problems in heterocyclic chemistry is the prediction and determination of the major site of alkylation in molecules containing more than one acceptor centre. This topic is discussed in a review by Duffin[124] in which many of the contradictory and erroneous conclusions which have resulted are pointed out. 4DMAP may undergo methylation[125] at either the ring nitrogen or the exocyclic nitrogen to give 8.3 (the resonance form of 8.2) or 8.4. However, the position of methylation could be determined by ^{1}H NMR spectroscopy; this technique was also chosen to obtain the rates of reaction.



8.3



8.4

If methylation had occurred at the exocyclic nitrogen to give 8.4 as the product, then the high-field region of the ^{1}H NMR (D_2O) spectrum would simply have revealed a singlet at *ca.* δ2.98 intergrating for six protons collapsing to another singlet lower field at *ca.* δ3.33[126] intergrating for nine protons. In other words, only one singlet and one doublet, corresponding to dimethyl phosphate (DMP) would appear in the non-aromatic part of the spectrum as the reaction progressed. However, this was not observed. Rather, two new singlets at δ3.30 and δ3.97 (intergrating for three and six protons, respectively) appeared along with the doublet for DMP at δ3.67 as the reaction proceeded. These singlets were assigned to the imminium ion $>C=\overset{+}{N}Me_2$, and to the uncharged N-methyl group >N-Me, within the ring system. The protons of the charged dimethyl imminium ion appear downfield (typical shift differences of Δδ0.3 ppm[127]) of the uncharged dimethylamino group.

Comparison of the ^{1}H NMR spectrum of the product with the ^{1}H NMR spectrum of authentic 4-dimethylamino-1-methyl pyridinium iodide confirmed our assignments. The methiodide was easily prepared following the procedure of Taddei *et al.*[125] This involved the addition of an equimolar amount of methyl iodide to a solution of 4DMAP in ethanol at room temperature. After one hour, the

crystalline product was collected, washed with ethanol and re-crystallized from propan-2-ol. The purity of the product was confirmed by m.p. determination and elemental analysis.

Kinetic measurements have been made for the reactions shown by eq.s 8.1 and 8.2, with D_2O, CD_3OD and CD_3CN as solvent, at a series of temperatures. Reaction 8.1 was also investigated in the absence of a solvent. The kinetics were carried out by sealing the mixed solutions of substrates in NMR tubes which were then heated in thermostatted water baths. The rate of the reaction was monitored by periodically withdrawing a tube from the bath, placing it in an ice-water bath (to arrest the reaction), recording the ^1H NMR spectrum of the sample, and returning the tube to the thermostatted bath. The reactions were slow ($k_2 = 10^{-4}$-$10^{-7} M^{-1}s^{-1}$) and therefore well-suited to ^1H NMR spectroscopy as a kinetic technique. The composition of the quarternization mixture was not dependent on the nature of the solvent and the results obtained in CD_3CN and CD_3OD agreed with the result mentioned above for D_2O. No mixed methylation products were found - accurate intergration measurements over-ruled any possibility of coalescing signals for the two isomers.

Although for the reaction in D_2O and CD_3CN, we chose to use the dimethylimminium product peak as a probe because it was well separated from the remaining absorption signals, in general, the other product signals could be employed as the intergration was sharply defined for each signal. Rate constants determined using either the doublet for DMP or the singlet for the $\geq$N-Me group confirmed this. For the reaction in CD_3OD, however, it was necessary to use the DMP product doublet or the $\geq$N-Me singlet as the solvent

peak overlapped with the imminium product peak. The progress of reaction (8.1), however, was more simply determined from the intergrated area of the signal of the N-methyl group of the pyridinium ion (δ4.43 in D_2O) and the intergrated areas of the signals of both methyl ester groups (D_2O: TMP, δ3.80; DMP, δ3.56).

Several attempts were made to prepare the product, N-methylpyridinium dimethylphosphate, from reaction 8.1 on a preparative scale, in order to hopefully, isolate a crystalline salt which could be characterized in the usual manner (m.p., ^1H NMR, elemental analysis, etc.). All attempts involved heating equimolar mixtures of pyridine and TMP in various solvents under reflux, or without a solvent at 65°C. In all cases the product separated as a syrupy liquid, which when kept under reduced pressure (*ca.* 0.5 mm Hg) for several hours, turned into the crystalline material. However, as soon as the sample was removed from the vacuum line, the crystalline material changed back to a syrupy liquid. In view of the highly hygroscopic nature of the salt, its melting point could not be determined and no reproducible results for elemental analysis could be obtained. The product, however, gave a ^1H NMR spectrum in good agreement with the expected pattern, with no indication of any side products or unreacted substrates.

Reaction 8.1 in CD_3CN occurred very slowly and only progressed significantly at 338 K. For this reaction at 298, 308 and 318 K, it was only possible to estimate approximate k_2 values using a single (and low) value of conversion, x after a suitably long time, and then calculate k_2 from eq. 8.3.

$$k_2 \leq {}^{1}/_{t} \frac{x}{a_o(a_o-x)} \qquad (8.3)$$

a_o = initial concentration of substrates

Similarly reaction 8.1 and 8.2 in CD_3OD, reaction 8.1 in the absence of solvent, and reaction 8.2 in CD_3CN, all at 298 K proceeded too slowly for reliable rate constants to be obtained by the NMR technique. However, in a number of cases, the "fast" reactions were repeated to determine the reliability of the results. In every instance these were satisfactory. Appendix IIIa and IIIb contain the results for the kinetic runs for reaction 8.1 and 8.2, respectively. The rate constants were calculated by plotting the $\frac{x}{a_o(a_o-x)}$ term against time and the slope of the linear plot, calculated by a least squares linear regression gave the value of the second-order rate constant $k_2 (M^{-1}s^{-1})$. Consistent with a second-order rate constant, no curvature was observed in the rate plots. The k_2 values are summarized in table 8.1 and 8.2 for the pyridyl and 4DMAP systems, respectively.

Having obtained the rate of reaction 8.1 and 8.2 in the various solvents at different temperatures, the results could then be analyzed on the basis of the Arrhenius equation (eq. 8.4).

$$\ln k_2 = \frac{-E_a}{RT} + \ln A \qquad (8.4)$$

where E_a = Activation energy (J $mole^{-1}$)

R = Gas constant (8.314 $JK^{-1}mole^{-1}$)

T = Absolute Temperature

A = Pre-exponential frequency factor.

The Arrhenius plots for the pyridine and 4DMAP systems are given in fig. 8.1 and 8.2, respectively. The activation energies were calculated from the slopes of the plots of $\ln k_2$ vs. $^1/_T$. Good linearity was obtained for both reactions. The Gibb's Free Energy of activation, $\Delta G^{\neq}$ at 298 K was then calculated from the relationship given in eq. 8.5.

$$k_2 = \frac{KTe}{h}^{-\Delta G^{\neq}/RT} \qquad (8.5)$$

where K = Boltzman constant

h = Planck constant.

For a reaction at a given temperature, the free energy of activation can then be related to the enthalpy and entropy of activation (eq. 8.6).

$$\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq} \qquad (8.6)$$

where $\Delta H^{\neq}$ = enthalpy of activation

$\Delta S^{\neq}$ = entropy of activation

For reactions in solutions, the volume of activation, $\Delta V^{\neq}$ is assumed constant and hence eq. 8.7 holds.

$$\Delta H^{\neq} = E_a - RT \qquad (8.7)$$

It is therefore possible to determine the required activation parameters ($\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$). These are given in tables 8.3 and 8.4.

The mixed solvent experiments were carried out with water-methanol and water-acetonitrile mixtures of various proportions. The solutions were prepared as shown in tables 8.5 and 8.6. The

rate constants, k_2, were determined at 298 K as described before and are given in tables 8.7 and 8.8. Appendix IIIc contains the results of the kinetic runs.

Table 8.1 Rate Constants[a] for reaction 8.1

Solvent	$k_2 \times 10^5 (M^{-1}s^{-1})$			
	298 K	308 K	318 K	338 K
D_2O	0.74	1.36	3.46	8.40
CD_3OD		0.12	0.38	1.96
CD_3CN[b]		0.014	0.037	0.25
No solvent		0.038	0.13	0.78

[a]The average values are reported in cases where the reaction was repeated.

[b]The values represent upper limits of the rate constants.

Table 8.2 Rate Constants[a] for reaction 8.2

Solvent	$k_2 \times 10^5 (M^{-1}s^{-1})$			
	298 K	308 K	318 K	333 K
D_2O	1.91	5.61	9.84	42.81
CD_3OD		0.71	1.40	6.21
CD_3CN		0.27	0.61	2.44

[a]The average values are reported in cases where the reaction was repeated.

Table 8.3 Activation Parameters[a] for reaction 8.1

Solvent	E_a $kJmol^{-1}$	$\Delta G^{\neq}$ $kJmol^{-1}$	$\Delta H^{\neq}$ $kJmol^{-1}$	$\Delta S^{\neq}$ $JK^{-1}mol^{-1}$
D_2O	51.9 ± 0.7	105.3 ± 3.0	49.3 ± 0.1	-177 ± 1.1
CD_3OD	79.6 ± 0.5	109.3 ± 1.7	77.0 ± 0.2	-108 ± 0.8
No solvent	86.3 ± 0.5	114.5 ± 1.5	83.6 ± 0.1	- 96 ± 0.7

[a]The values for $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the average of the values calculated at each temperature.

Table 8.4 Activation Parameters[a] for reaction 8.2

Solvent	E_a $kJmol^{-1}$	$\Delta G^{\neq}$ $kJmol^{-1}$	$\Delta H^{\neq}$ $kJmol^{-1}$	$\Delta S^{\neq}$ $JK^{-1}mol^{-1}$
D_2O	71.3 ± 0.7	101.5 ± 1.6	68.6 ± 0.1	-105 ± 1.1
CD_3OD	74.8 ± 0.7	107.7 ± 1.5	72.0	-110 ± 1.0
CD_3CN	76.1 ± 0.3	109.7 ± 1.5	73.3 ± 0.6	-113 ± 1.7

[a]The values for $\Delta G^{\neq}$, $\Delta H^{\neq}$ and $\Delta S^{\neq}$ are the average of the values calculated at each temperature.

Table 8.5 Composition of D_2O/CD_3OD solutions at 298 K

Mole % D_2O: CD_3OD	mole D_2Ox10^3	vol D_2O (ml)	mole CD_3ODx10^3	vol CD_3OD (ml)
80:20	17.68	0.320	4.45	0.180
60:40	11.05	0.200	7.42	0.300
40:60	6.35	0.115	9.52	0.385
20:80	2.76	0.050	11.12	0.450

Table 8.6 Composition of D_2O/CD_3CN solutions at 298 K

Mole % D_2O: CD_3CN	mole D_2Ox10^3	vol D_2O (ml)	mole CD_3CNx10^3	vol CD_3CN (ml)
92:8	22.07	0.400	1.91	0.100
81:19	16.55	0.300	3.81	0.200
66:34	11.03	0.200	5.72	0.300
24:76	2.76	0.050	8.58	0.450

Table 8.7 Rate Constants in D_2O/CD_3OD mixtures at 298 K

Mole % D_2O	Pyridine + TMP $k_2 \times 10^6 (M^{-1}s^{-1})$	4DMAP + TMP $k_2 \times 10^5 (M^{-1}s^{-1})$
100	7.40	1.91
80	3.41	1.06
60	1.22	0.63
40	0.67	0.50
20	0.60	0.33

Table 8.8 Rate Constants in D_2O/CD_3CN mixtures at 298 K

Mole % D_2O	Pyridine + TMP $k_2 \times 10^6 (M^{-1}s^{-1})$	4DMAP + TMP $k_2 \times 10^5 (M^{-1}s^{-1})$
100	7.40	1.91
92	4.03	1.05
81	2.39	0.83
66	1.26	0.62
24	0.44	0.33

Fig. 8.1 Arrhenius plot for reaction 8.1 in D_2O, CD_3OD and in the absence of solvent

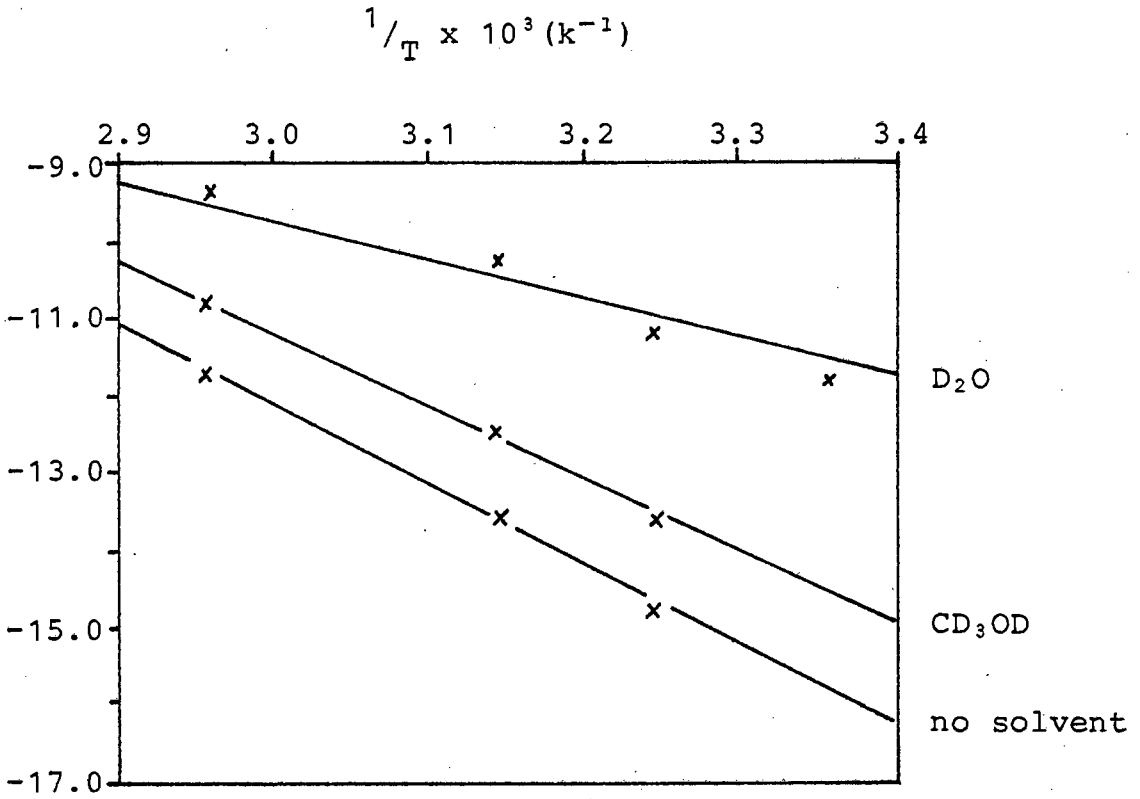
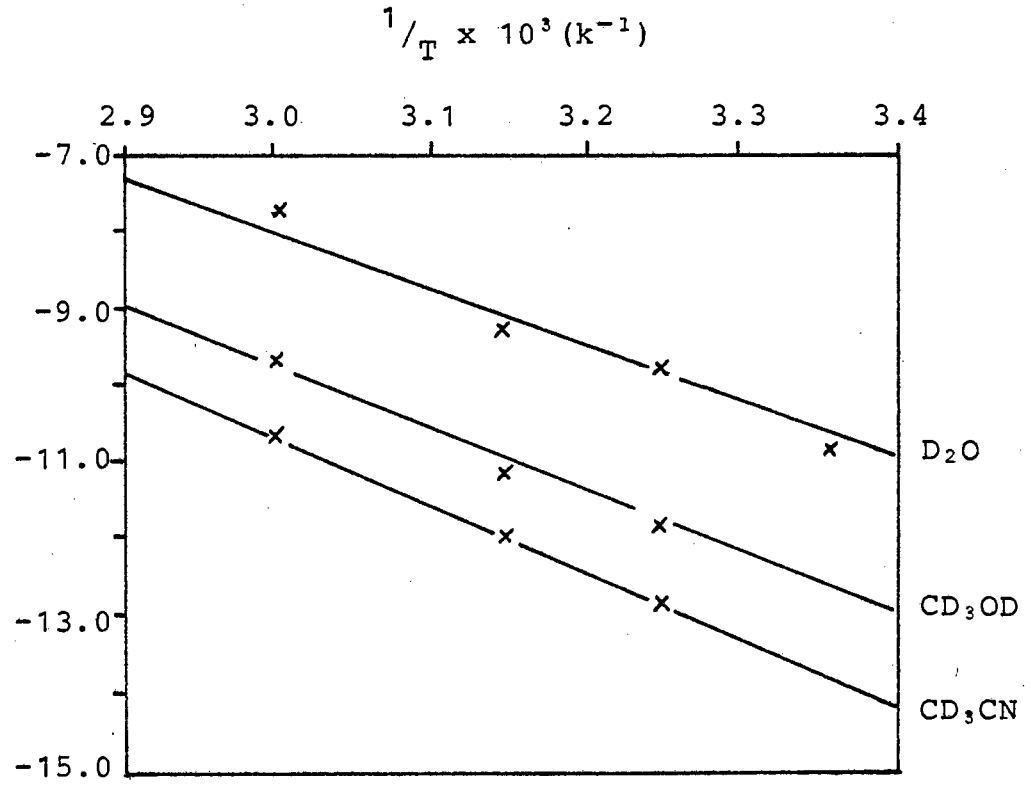


Fig. 8.2 Arrhenius plot for reaction 8.2 in D_2O, CD_3OD and in CD_3CN



8.3 DISCUSSION

8.3.1 REACTIONS IN PURE SOLVENTS

As expected, the introduction of the NMe_2 substituent *para* to the pyridyl nitrogen enhances the reactivity of the ring N centre and this is clearly illustrated by the k_2 values for reaction 8.2 which are of the order 3 - 18 times greater than the corresponding values for reaction 8.1. Table 8.9 gives the k_{rel} values in the different solvents. In D_2O and CD_3OD, 4DMAP is on average only 3.2 and 4.8 times more reactive than pyridine. In CD_3CN, however, 4DMAP is 17.9 times more reactive than pyridine. This marked difference in the k_{rel} values between hydrogen bonding and non-hydrogen bonding solvents reflects the importance of solvation when reactions take place in solution. In an ideal solvent, neither the activated complex nor the reactants are solvated and such a system therefore approaches the gas phase condition. Acetonitrile in this instance tends towards the gas phase reaction where the observed difference in reactivity of 4DMAP and pyridine is due to the difference in the availability of the electron pair on nitrogen - the solvent remaining "inert". Hydrogen bonding therefore confers decreased selectivity on methyl transfer to two nitrogen centres having a difference in basicity of 4.39 pK_a units.[127]

A consideration of the effect of solvent on both reaction 8.1 and 8.2 is one of the fundamental aims of our study. These k_{rel} values, with k_{CD_3CN} chosen as the reference solvent are given in table 8.10. The rate of methyl transfer to pyridine in CD_3OD and D_2O is, respectively 9.4 and 95.3 times faster than the corresponding rate in CD_3CN. Similarly for reaction 8.2, if k_{CD_3CN} is taken as unity,

Table 8.9 Relative rate of methylation of 4DMAP to pyridine

Solvent	Temperature (K)	k_{rel}	k_{rel} ave.
D_2O	298	2.7	
	308	4.1	3.2
	318	2.7	
CD_3OD	308	5.9	4.8
	318	3.7	
CD_3CN	308	19.3	17.9
	318	16.5	

Table 8.10 Relative rate constants[a] for methylation of pyridine and 4DMAP

	Pyridine + TMP			4DMAP + TMP			
	k_{rel}		av. k_{rel}	k_{rel}			av. k_{rel}
T(K) / Solvent	308	318		308	318	333	
CD_3CN	1	1		1	1	1	
CD_3OD	8.6	10.3	9.4	2.6	2.3	2.5	2.5
D_2O	97.1	93.5	95.3	20.8	16.1	17.5	18.1

[a]All rate constants are relative to reaction in CD_3CN.

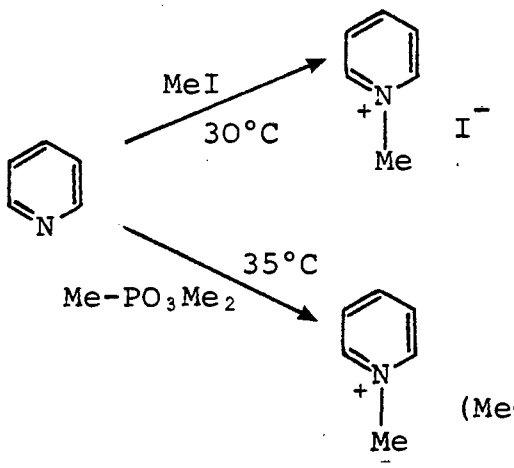
then the reactions in CD_3OD and D_2O are respectively 2.5 and 18.1 times faster.

According to Ingold's classification,[128] both reactions 8.1 and 8.2 belong to the nucleophilic substitution reaction "class C" along with the well-known Menshutkin reaction. "Class C" reactions involve two neutral substrates which react to form an activated complex in which there is separation of unlike charges (eq. 8.8).

$$Y + R{-}X \xrightarrow{S_N2} Y^{\delta+}\cdots R\cdots X^{\delta-} \qquad (8.8)$$

Ingold's qualitative theory of solvent effects on reaction rates for "class C" reactions, predicts that an increase in solvent polarity will cause a large increase in the rate of reaction. Interestingly enough, one of the first (1890) systematic investigations on the effect of solvent on reaction rates was the reaction of triethylamine with ethyl iodide carried out in twenty-two solvents.[129] Despite this and also the fact that the quarternization of tertiary amines by alkyl halides has been studied by many physical methods over a long period of time, a survey of the literature revealed the surprising fact that very few results in hydroxylic solvents have been reported. Only recently has a study of the Menschutkin reaction in acetonitrile-methanol mixtures been investigated by Kondo *et al.*[130] Kondo's results for the reaction of pyridine and methyl iodide in acetonitrile-methanol mixtures are directly relevant to our study and are summarized together with our result for reaction 8.1 in scheme 8.1.

Scheme 8.1



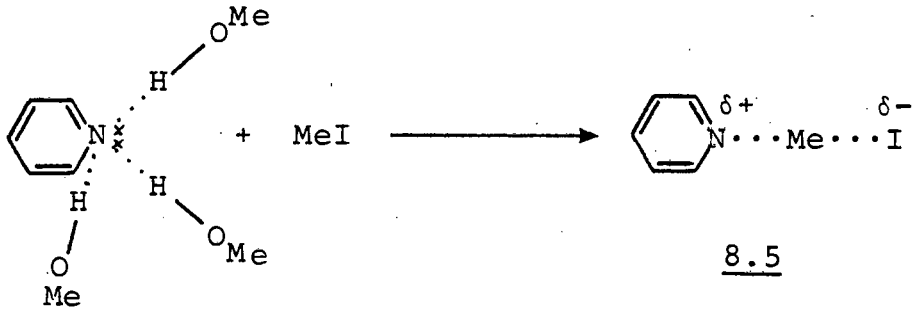
k_{CH_3OH}/k_{CH_3CN} = 0.053[a]

k_{CD_3OD}/k_{CD_3CN} = 8.6[b]

[a]Ref 130

[b]This work

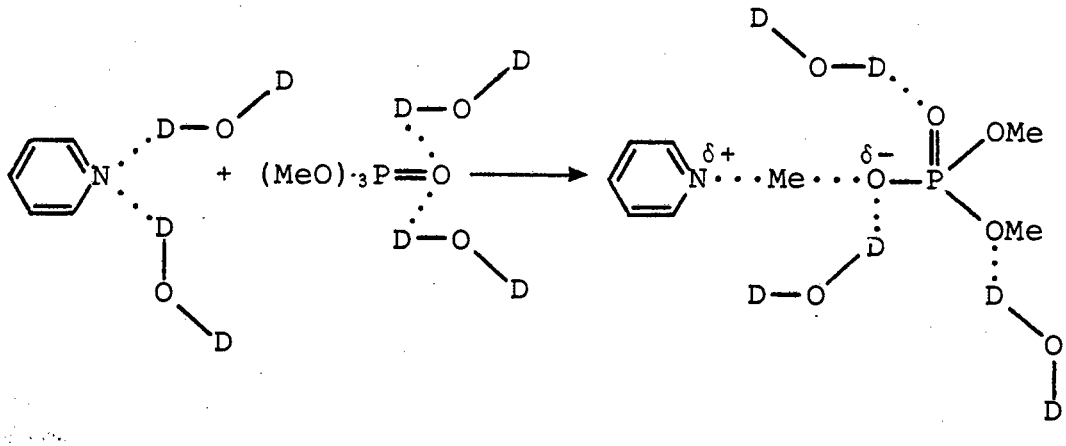
Ignoring the 5°C increase in temperature and the use of deuterated solvents, our study reveals a very different solvent dependence compared to Kondo's results - the "switch over" factor from using methyl iodide to trimethyl phosphate as methylating agent being 162 fold. This result can be rationalized by considering the effect of solvent on the reactants and on the activated complex. Firstly, Kondo's results show that the methylation of pyridine by methyl iodide is *ca.* 19 times faster in acetonitrile than in methanol. The reason for this is that hydrogen bonding to pyridine occurs in methanol,[131] thus decreasing the nucleophilicity of the substrate, which has to undergo desolvation before it can develop bonding interactions with the carbon atom. This reaction (eq. 8.9) is an example where one of the initial reactants is more strongly solvated than the activated complex.



(8.9)

8.5

Secondly, reaction 8.1 is *ca.* 8.6 times faster in CD_3OD than in CD_3CN. This suggests that the transition state (TS) 8.6 in eq. 8.10, is favoured more by CD_3OD than by CD_3CN. As in the previous case, hydrogen bonding has an effect on pyridine nucleophilicity and in addition, TMP itself is also strongly hydrogen bonded.[132] However, although both effects will cause decceleration in the rate of reaction, the effect of hydrogen bonding on T.S. solvation seems to be much greater than the effect of hydrogen bonding on substrate solvation.



(8.10)

8.6

For both eq.s 8.9 and 8.10, the leaving group departs as an anion and it is expected that solvation of the leaving group will be more effective in protic solvents which can act through hydrogen bonding. However, the nature of the leaving group is of fundamental importance and while it has been demonstrated[133] that the affinity of the phosphate group for hydroxylic solvents increases rapidly in the order phosphate triester < diester < monoester, the large "soft" iodide anion in which charge is dispersed,[134] is less amenable to hydrogen bonding. We believe hydrogen bonding to the leaving phosphate anion is responsible for the observed variation in the solvent effects in the pyridine/TMP system when compared to the pyridine/MeI system.

The rate constant ratio k_{D_2O}/k_{CD_3CN} is simply a more pronounced example of the k_{CD_3OD}/k_{CD_3CN} ratio discussed above and it illustrates the better proton donor ability of water over methanol.[135]

As a corroborative comment, our own control results for the methylation of 4DMAP by methyl iodide, support Kondo's results. As the reaction in CD_3CN proceeded almost instantaneously, no rate constant could be obtained by our kinetic technique. However, on transfer from CD_3CN to CD_3OD, the reaction was slowed down sufficiently to determine the rate constant. These results appear in Appendix IIId. The k_2 value of $1.29 \times 10^{-5} M^{-1} s^{-1}$ (298 K) corresponds well to the rate constant $k_2 = 2.97 \times 10^{-5} M^{-1} s^{-1}$ (303 K) obtained for the reaction of pyridine with methyl iodide in methanol.[130]

Although for reaction 8.2, the changes in rate are correlated with

changes in activation energy, the increase in the E_a values in the order D_2O < CD_3OD < CD_3CN is not very great. Nevertheless, it is definite and consistent for both series, being markedly more noticeable for pyridine than for 4DMAP. However, a gross disparity is found between the k_2 and E_a values for reaction 8.1 when compared to reaction 8.2 in D_2O. The faster reaction (8.2) is not paralleled by a concomitant lower activation energy. This immediately suggests that the pre-exponential factor in the Arrhenius equation plays a more dominant role in determining the relative reactivity of these two substrates. A very convenient way of representing the relationship between the kinetic and activation parameters for a series of related reactions, is to plot the log k_2 values for a given temperature against the corresponding E_a values.[136] If when comparing two reactions, the line joining the two corresponding points on the diagram has a slope of 2.303 RT, then, the difference in rate constant is due entirely to the difference in E_a. Figures 8.3 and 8.4 give these plots for reactions 8.1 and 8.2, respectively. For reaction 8.2 at all four temperatures, the line joining the point for the reaction in D_2O to the point corresponding to the reaction in CD_3OD is less steep than the standard slope of 2.303 RT and even less steep for the D_2O-CD_3CN or CD_3OD-CD_3CN line. This is interpreted by the probability factor P, which is therefore greater for the faster reaction (i.e. D_2O as compared to CD_3OD or CD_3CN and CD_3OD as compared to CD_3CN). The large deviation from the standard line illustrates that the change in rate constant is due more to P than to E_a. It seems reasonable to attribute this to a decreased probability in favourably orientated collisions in going from D_2O to CD_3OD to

CD_3CN. Conversely for reaction 8.1 the line joining the point for the reaction in D_2O to the point corresponding to the reaction in CD_3OD is more steep than the standard slope. According to Hinshelwood,[136] the probability factor P is greater for the slower reaction (i.e. in CD_3OD as compared to D_2O).

The probability factor is manifested directly in the entropic term $\Delta S^{\neq}$, and is closely related to the solvation of the transition state in this S_N2 reaction. Tables 8.3 and 8.4 show that all entropies of activation are large negative values which is typical for the bimolecular mechanism. The entropy of activation for the methylation of pyridine (reaction 8.1) in D_2O is exceptionally low indicating considerable increase in hydration requirements when moving from substrates towards the transition state. This unfavourable entropy factor is therefore responsible for the lower reactivity of pyridine, despite the less positive value of $\Delta H^{\neq}$ for this reaction. Reaction 8.1 has a less negative entropy in CD_3OD than in D_2O, and still less negative in CD_3CN. This strongly marked solvent dependence on the $\Delta S^{\neq}$ value for reaction 8.1 suggests a highly polar transition state, having a high demand for solvation, and, in particular, for stabilization *via* hydrogen bonding to solvent molecules (see 8.6). It can be concluded therefore, that reaction 8.1 involves a relatively "late" transition state, with large charge fractions being localized on pyridine nitrogen and phosphate oxygen atoms. It is worth mentioning at this point that the partition coefficient for transfer from a non-polar medium to water is *ca.* 4×10^4 greater for dimethyl phosphate than the corresponding value for TMP.[133] We believe that the difference of *ca.* 44 $JK^{-1}mol^{-1}$ between the $\Delta S^{\neq}$ values for methylation of pyridine

in water by TMP and methyl iodide[130] reflects the difference in hydration requirements of the departing dimethyl phosphate and iodide anions, respectively.

The entropic trend observed for methylation of pyridine is not paralleled in the $\Delta S^{\neq}$ values for the 4DMAP methylation reaction. The $\Delta S^{\neq}$ values for reaction 8.2 do not vary much, but become slightly more negative in the order D_2O < CD_3OD < CD_3CN. The presence of a hydrogen bonding solvent (D_2O and to a lesser extent CD_3OD) in the transition state to assist dimethyl phosphate departure is obviously not so important in reaction 8.2. We believe that there are two possible reasons for the difference in the changes of $\Delta S^{\neq}$ values for these two reactions. Firstly, the reactivity-selectivity principle imputes greater selectivity to less reactive reagents. The NMe_2 substituent could therefore enhance the reactivity of the nucleophilic N centre as well as decrease the selectivity of the reaction i.e. the more reactive substrate is less dependent on solvent effects. The second possible reason relates to the structural differences between the ionic products of reactions 8.1 and 8.2. In reaction 8.1, the cation developed, (N-methyl-pyridinium), has its charge localized on a single atom. As such, it should interact strongly with solvent water and hence contribute to the total hydration requirements of the transition state. In reaction 8.2, however, the resonance-stabilized cation is developed (see resonance structures 8.2 and 8.3), and the interactions between such a large delocalized ion with water would be expected to be significantly decreased.

The results presented in table 8.3 show that the activation enthalpy

for reaction 8.1 in CD_3OD is higher than that for the reaction in D_2O. The reason for this is that D_2O being more polar than CD_3OD can form hydrogen bonds more easily with the polar transition state. Thus the activated complex is more stable in D_2O than in CD_3OD. The free entropy of activation $\Delta S^{\neq}$, has already been discussed in relation to the pre-exponential factor in the Arrhenius equation. However, when $\Delta S^{\neq}$ is considered alongside the $\Delta H^{\neq}$ values, it is apparent that these two parameters act in opposition to each other. But the $-T\Delta S^{\neq}$ terms are not large enough to outweigh the $\Delta H^{\neq}$ terms and therefore the free energy of activation $\Delta G^{\neq}$, reflects the same trend as the enthalpy values.

The above reasoning can be used to explain the lower $\Delta H^{\neq}$ value in D_2O than in CD_3OD or CD_3CN for reaction 8.2. However, although the $\Delta S^{\neq}$ values now act in the same direction as the $\Delta H^{\neq}$ values, the $\Delta S^{\neq}$ values for methylation of 4DMAP in D_2O, CD_3OD and CD_3CN are nearly the same. The change in $\Delta S^{\neq}$ for transferring reaction 8.2 from D_2O to CD_3OD is only $-5\ JK^{-1}mole^{-1}$ compared to about $70\ JK^{-1}mole^{-1}$ for reaction 8.1. In spite of our earlier proposals regarding possible reasons for the variation in the $\Delta S^{\neq}$ values between reaction 8.1 and 8.2, it must not be overlooked that $\Delta S^{\neq}$ values are more susceptible to experimental error than either $\Delta G^{\neq}$ or $\Delta H^{\neq}$ parameters.

On comparing the k_2 values of reaction 8.1 in D_2O, CD_3OD and CD_3CN as solvents, with the reaction carried out with no solvent, it is seen that the reaction with no solvent is slower than the reaction in D_2O and CD_3OD but faster than the reaction in CD_3CN. This indicates that the effectiveness of solvating (hence stabilizing)

the TS for reaction 8.1 decreases in the following order:

$$D_2O > CD_3OD > (TMP/PY) > CD_3CN \qquad (8.11)$$

The poor ability of the substrates themselves to solvate the TS of reaction 8.1 is demonstrated by calculating the corresponding activation parameters. Table 8.3 shows that the lower reactivity in the absence of solvent than in D_2O or CD_3OD is due to a high value of $\Delta H^{\neq}$. This is most likely due to the less effective solvation of the TS. Weaker and non-specific solvation (no hydrogen bonding possible) results, however, in a significantly less negative value of entropy of activation (-81 $JK^{-1}mole^{-1}$) indicating less rigorous ordering of molecules around the polar TS.

8.3.2 REACTIONS IN MIXED SOLVENTS

The experiments using mixed solvents were designed in the hope of determining whether water (as a protic solvent) plays a "discreet" (specific) function as opposed to a general bulk solvent function during methyl transfer from TMP to pyridine and 4DMAP.

Plots of $\ln k_2$ versus mole % D_2O for reaction 8.1 and 8.2 in aqueous CD_3OD and aqueous CD_3CN are shown in fig. 8.5. All the plots are monotonic with no large variation in rate values. This indicates that k_2 is simply proportional to the molar fraction of water in the mixture and there is no convincing evidence for any breakpoint which could suggest some important changes in the structure of the bulk solvent system.

Although water/acetonitrile mixtures *per se* have been investigated by a wide variety of physico-chemical techniques,[137] and studies of water/methanol mixtures have also been reported,[138] our work has been of an investigatory nature, aimed at determining the effect of solvent on the methyl transfer reaction and not the effect of added solvent on solvent-solvent interactions in binary mixtures.

It is of interest to point out that the rate constant for reaction 8.1 decreases only *ca.* 3 times on transfer from pure D_2O to aqueous CD_3CN (81 mole % D_2O). Similarly for reaction 8.2, this decrease is *ca.* 2.3-fold (see tables 8.7 and 8.8). For 2-adamantyl nosylate, it has been reported[139] that the rate constant of hydrolysis decreases *ca.* 156-fold on transfer from H_2O to aqueous CH_3CN (81 mole % H_2O).* Or expressed relatively, reaction 8.1 and 8.2 are 52 and 60 times respectively, less sensitive to the proportion of water in aqueous acetonitrile when the reactions are transferred from pure water to aqueous acetonitrile (81 mole % H_2O). The large solvent dependence for the hydrolysis of 2-adamantyl nosylate is a reflection of the type of this reaction (S_N1) and the charge

*Although we are aware that some authors have concluded that D_2O is more structured than H_2O at comparable temperatures,[140] and further, that the D_2O/H_2O comparison has been extended to the effect on $\Delta H^{\neq}$ and $\Delta S^{\neq}$ values in the hydrolysis of *t*-butyl chloride,[141] this present comparison is of a qualitative nature only and no distinction is therefore necessary between the deuterated and non-deuterated solvents.

development during the rate-determining unimolecular ionization. Solvation of the cation in the resulting ion pair will be more favourable in protic solvents. The greater the energy of solvation of the ions so formed, the greater the recovery of the energy necessary to effect the initial ionization, and, hence the more favourable the reaction.

Reaction 8.1 and 8.2 are examples of one of the most common charge types of the S_N2 reaction and involve the reaction of a neutral nucleophile with a neutral electrophile. These reactions are faster in polar protic solvents (e.g. D_2O) than in dipolar aprotic solvents (e.g. CD_3CN) because of solvation of the partial charge development in the transition state.

8.4 CONCLUSION

The results presented in this chapter support the fundamental role of solvation in an S_N2 reaction involving the triester → diester change at the phosphate substrate. Water and methanol which are strong hydrogen bond donors favour the reaction, relative to dipolar aprotic solvents such as acetonitrile. In this respect, the dialkyl phosphate moiety represents an interesting leaving group in an S_N2 process, responding to changes in solvent structure in a manner qualitatively different from such typical leaving groups as halide ions. The fact that chemical changes which result in a decrease of the degree of esterification of phosphoric acid are highly favoured in aqueous media, may be relevant to the widespread occurrence of phosphoric mono- and diesters in nature, with the conspicuous absence of the naturally occurring phosphoric triesters.

Although methyl transfer from TMP to pyridine and to 4-(dimethyl-amino)-pyridine was fastest in water, our experiments using binary mixtures of water/methanol and water/acetonitrile reveal that the interactions of the leaving phosphate anion with water are of a general nature. The function of water in the reaction is therefore in the capacity of a bulk protic solvent rather than a specific hydrogen bond donor.

Figure 8.3 Plots of E versus $\log_{10} k_T$ at different temperature for reaction 8.2

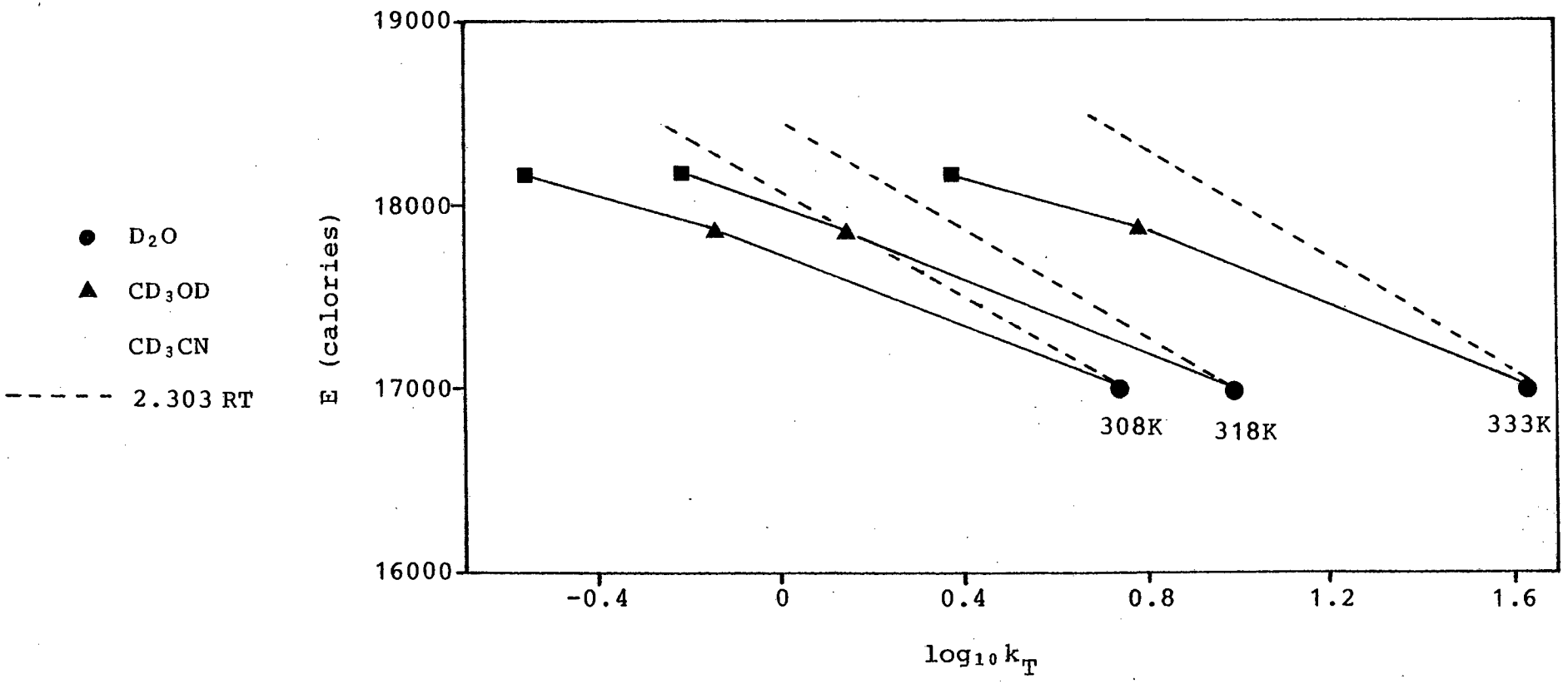


Figure 8.4 Plots of E versus $\log_{10} k_T$ at different temperatures for reaction 8.1

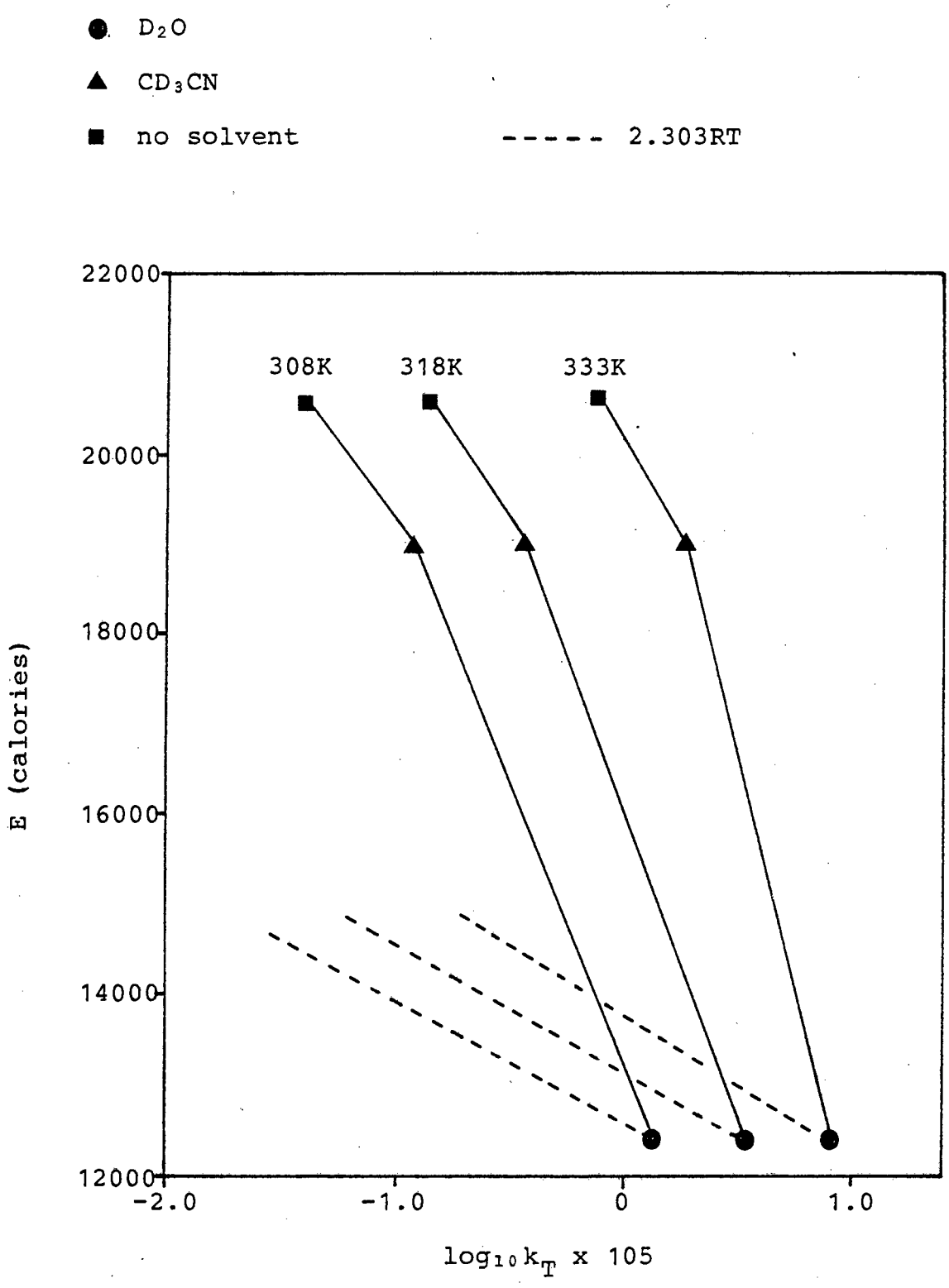
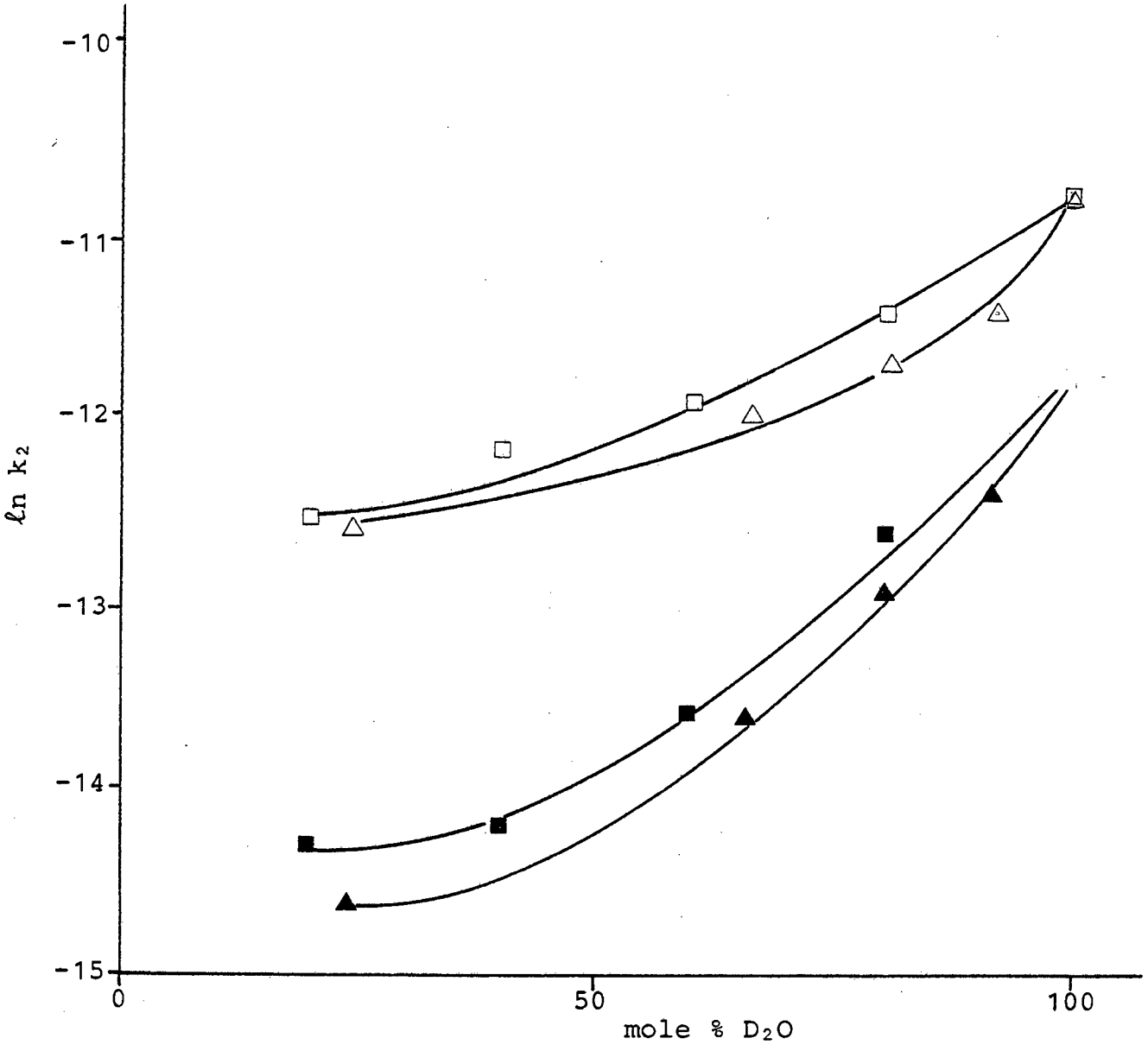


Figure 8.5 Plots of $\ell n\ k_2$ versus mole composition of solvent for reactions 8.1 and 8.2 at 25°C

Reaction 8.1: ■ D_2O/CD_3OD; ▲ D_2O/CD_3CN

Reaction 8.2: □ D_2O/CD_3OD; △ D_2O/CD_3CN



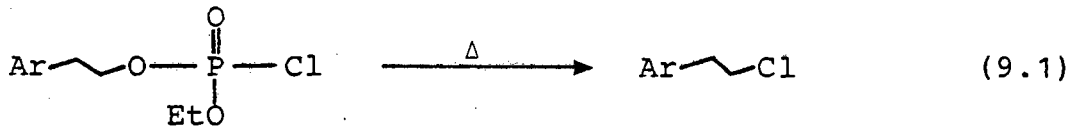
Chapter 9

Fragmentation of β-Arylethyl Phosphate Esters

9.1 INTRODUCTION

Anchimeric assistance or neighbouring group participation are terms describing intramolecular nucleophilic displacement reactions which are particularly rapid because the nucleophile and the leaving group are present in the same molecule. Winstein describes the participation of a functional neighbouring group and its associated electron cloud in nucleophilic displacement processes at a nearby centre as 'a general phenomenon',[142] but these processes are not only found in specially designed organic model compounds, they also occur in many biological processes.[143]

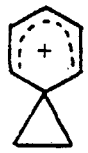
During our preliminary work on synthetic methods for preparation of model phosphate esters (ch. 2), we have observed that ethyl (β-phenylethyl)phosphorochloridate, 9.1 (Ar = C_6H_5), decomposes thermally yielding β-phenylchloroethane (eq. 9.1). The



(9.1)

9.1

identification of β-phenylchloroethane as one of the fragmentation products enabled us to speculate on the mechanism of the reaction (eq. 9.1), which almost certainly proceeds with neighbouring participation of the β-phenyl group and involves the bridged phenonium ion 9.2 as a reactive intermediate.



9.2

Nucleophilic assistance by the β-aryl group is a well known example of neighbouring group participation in the nucleophilic displacement at carbon[144] and was documented as early as 1949 by Cram.[145] Cram was the first to provide evidence for the existence of a cyclic bridged ion as a discrete molecular species (a carbocyclic 3-membered carbonium ion) in the Wagner-Meerwein rearrangement of isomers of 3-phenyl-2-butanol, and later, the first observation (NMR technique) of arylonium ion formation *via* aryl participation in strong acid solution was achieved.[146] The general reaction (9.2) has, in fact, been the object of detailed kinetic, mechanistic and stereochemical investigations[147] and has usually involved organic sulfonates (X = p-toluenesulfonate, p-bromobenzenesulfonate) or halides (X = halogen) as substrates.

9.3 9.4 (9.2)

Recently, several reports regarding nucleophilic displacement at the α-carbon atom of organic phosphates have appeared in the literature.[148] In addition, although there is a growing interest in the application of (β-arylethyl) phosphates (as blocking groups) in oligonucleotide synthesis,[149] no reactions involving phosphate esters of type 9.3 (X = OP(O)ZY) and proceeding *via* intermediates of type 9.4 have been investigated.

Nucleophilic displacement at the α-carbon atom of organic phosphates is a recurring theme in this project and has been discussed in ch.s 4 and 8. In ch. 4, the model compound dimethyl-(2-pyridylmethyl) phosphate (A), incorporated both the nucleophilic and electrophilic centres (although the methyl transfer raction was shown to be bimolecular), whereas in ch. 8, the electrophilic centre (α-carbon or methyl group of TMP) and the nucleophilic centre (pyridine or 4-dimethylamino pyridine) were in two chemically different compounds. (β-Arylethyl) phosphates 9.3 (X = OP(O)ZY), can again provide both the nucleophilic and electrophilic (α-carbon atom) centres in the one molecule and moreover, because of the known[150] ability of P^V derivatives to reduce the coordination number of phosphorus (formation of a "metaphosphate" species), the substrate molecule itself could be expected to yield a nucleophile Y^-. Contrary to most of the previous studies reported in the literature which have been carried out under solvolytic conditions so that the arenium ion 9.4 was trapped by a molecule of nucleophilic solvent, we believe that substitution in 9.3 (X = OP(O)ZY), may occur under non-solvolytic conditions. This fortuitously reduces the problems associated with separating anchimerically assisted and anchimerically unassisted (i.e. solvent assisted) effects. Our preliminary result with ethyl (β-phenylethyl)phosphorochloridate (eq. 9.1) can be considered a specific example of the collapse of a phosphate RO-P(O)ZY proceeding with expulsion of the metaphosphate species ZPO_2, and with formation of an alkyl derivative RY.

The aim of this study was to prepare a number of (β-arylethyl) phosphates with the intention of investigating reaction (9.2) in

more detail, particularly in terms of the bonding changes at the phosphorus atom during the fragmentation step. As an extension of this work, we were also interested in the electron impact-induced fragmentation in this class of compounds.

9.2 SYNTHESIS OF (β-ARYLETHYL)PHOSPHOROCHLORIDATES AND RELATED COMPOUNDS

In addition to ethyl (β-phenylethyl)phosphorochloridate, 9.1a (the synthesis is discussed in ch. 2.5), a range of substrates having the general formula RO-P(O)ZY were synthesized (see table 9.1) in the course of a search for the main requirements for reaction 9.2 where X = OP(O)ZY. The substrates 9.1b-h are related to 9.1a and were designed to vary either the β-("neighbouring") group, or the leaving group Y at phosphorus.

If 9.1a is considered the 'standard' compound, then the formulation of substrate 9.1b as a reactant should illustrate the importance of the leaving group at phosphorus in the anchimerically assisted reaction. Substrate 9.1c can be considered to contain an enhanced neighbouring group effect compared to 9.1a. Substitution of chlorine in 9.1a, 9.1c and 9.1g by the p-nitrophenoxy group gives substrates 9.1d, 9.1e and 9.1h, respectively. The formulation of (β-arylethyl) p-nitrophenyl phosphates as substrates for this study arose from the need to determine whether it was the leaving ability (nucleofugality) of Y (in the fragmentation step) and/or the nucleophilicity of Y (in the product formation step) which was critical for the fragmentation to occur.

Table 9.1 Substrates RO-P(O)ZY prepared for this study

	R	Z	Y
9.1a	$PhCH_2CH_2$	EtO	Cl
9.1b	$PhCH_2CH_2$	Cl	Cl
9.1c	$PhCH_2CH_2$	$PhCH_2CH_2O$	Cl
9.1d	$PhCH_2CH_2$	EtO	PNPO
9.1e	$PhCH_2CH_2$	$PhCH_2CH_2O$	PNPO
9.1f	$AnCH_2CH_2$	Cl	Cl
9.1g	$AnCH_2CH_2$	$AnCH_2CH_2O$	Cl
9.1h	$AnCH_2CH_2$	$AnCH_2CH_2O$	PNPO
9.1i	$PhCH_2CH_2$	EtO	EtO

An = $MeO-C_6H_4$

Substrates 9.1f, 9.1g and 9.1h are the p-methoxy analogues of 9.1b, 9.1c and 9.1e, respectively. The p-anisyl group participates in nucleophilic displacement more strongly than the phenyl group[151] as it is more strongly electron donating. We therefore hoped to manipulate the electronic environment of the substrates in such a way so as to favour neighbouring group participation in reaction 9.2. Diethyl (β-phenylethyl) phosphate 9.1i, having no good leaving group at phosphorus, was synthesized as a control substrate. We expected that this compound would be unreactive compared to its phosphorochloridate or phosphorodichloridate analogues 9.1a and 9.1b, respectively.

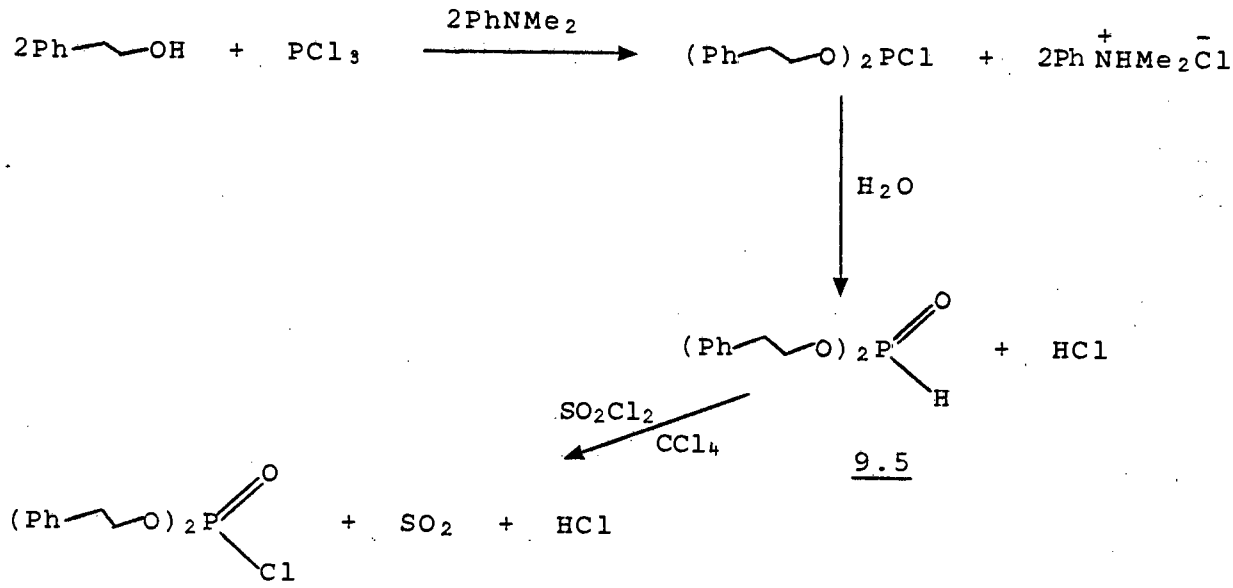
Substrates 9.1a-i were prepared from phosphorus trichloride, phosphorus oxychloride or mono- or diethylphosphorochloridate and the corresponding alcohols according to established procedures.[152] The synthesis of ethyl (β-phenylethyl)phosphorochloridate 9.1a has been described in ch. 2.5. As was the case for this compound, the major problem we encountered during the synthesis of the remaining compounds involved the purification of the final product. All compounds 9.1a - 9.1i are liquids at room temperature and distillation of the crude product was therefore an obvious purification procedure. However, because we had already observed fragmentation of 9.1a during distillation (see ch. 2.5) and because of uncertainty regarding the thermal stability of the other substrates, we were reluctant in many cases to resort to using distillation as the means of purification.

(β-Phenylethyl)phosphorodichloridate, 9.1b, was prepared by adding an etheral solution of β-phenylethanol (x mol) dropwise,

with cooling and stirring, to a solution of phosphorus oxychloride (1.5x mol) in ether. The reaction was instantaneous. Removal of the solvent gave a pale-yellow oil. This was immediately distilled and pure (β-phenylethyl)phosphorodichloridate was collected at 100—103°C/.4 mm as a colourless oil. Elemental analysis and ^{1}H NMR spectroscopy confirmed the purity of the product.

Bis-(β-phenylethyl)phosphorochloridate, 9.1c, was prepared by the reaction of phosphorus trichloride with β-phenylethanol in the presence of a tertiary base, followed by hydrolysis to bis-(β-phenylethyl) phosphite 9.5. Treatment of the phosphite with sulphuryl chloride, under an atmosphere of nitrogen, resulted in a colourless oil, which was shown by ^{1}H NMR spectroscopy and elemental analysis to be the required product. The reaction is shown in scheme 9.1.

Scheme 9.1



Similarly bis-[β-(p-methoxyphenyl)ethyl]phosphorochloridate, 9.1g, was obtained from the corresponding phosphite. The 'phosphite' approach to the synthesis of 9.1c and 9.1g was attractive because it involved the preparation of an intermediate - the phosphite 9.5, which is a more stable phosphorus compound than the phosphorochloridate derivative, both in respect to nucleophilic cleavage and to thermal decomposition. Therefore the intermediate could be purified before proceeding with the second step of the reaction, thus lessening the need for distillation of the phosphorochloridate - the thermal stability of which was questionable. Although there has been a report on complete decomposition of phosphites[153] during distillation, bis-(β-phenylethyl) phosphite was purified by distillation as a fluorescent oil, b.p. 173 - 175°C/.2 mm. During the synthesis of bis-[β-(p-methoxyphenyl)ethyl] phosphite, the amount of alcohol remaining in the reaction mixture was monitored by TLC, and only after stirring the mixture for 16 h at room temperature, was water added. After work up, the phosphite was obtained as a colourless oil which was proven to be pure according to elemental analysis and ^{1}H NMR spectroscopy.

The synthesis of [β-(p-methoxyphenyl)ethyl]phosphorodichloridate, 9.1f, was attempted using exactly the same procedure as that used for 9.1**b**. The synthesis of the starting alcohol, β-(p-methoxyphenyl)ethanol was based on a method used for the reduction of phenylacetic acid to β-phenylethanol by lithium aluminium hydride.[154] However, 9.1f could not be obtained in an analytically pure form as the burgundy-coloured crude product which formed after removal of excess of $POCl_3$ and solvent, decomposed at room temperature under vacuum after a few hours and also after one week in a

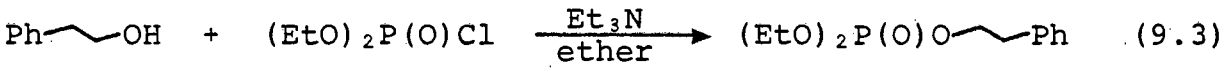
refrigerator. It was, however, possible to obtain a ^{1}H NMR spectrum of the crude product and this showed a triplet at δ2.02 for the methylene protons β to phosphorus, a singlet at δ2.77 for the methoxy protons, a doublet of triplets at δ3.18-3.67 for the α-methylene protons and a doublet of doublets at δ5.70-6.30 for the aromatic protons of the *para* methoxy substituted phenyl ring. The intergration for these signals was in the expected 2:3:2:4 ratio. Decomposition of 9.1f produced dark material, giving off fumes of hydrogen chloride. In order to separate the organic component of the mixture from the inorganic products, aqueous sodium hydroxide was added and the mixture heated under reflux for 5 h. The solid which separated out was purified by column chromatography (chloroform : pet. ether, 2:1) yielding an amorphous, highly insoluble solid. The ^{1}H NMR (DMSO-d_6, 120°C) and IR spectra of this product were identical to those of poly-(p-methoxystyrene), obtained by treating p-methoxystyrol with concentrated sulphuric acid.

Compound 9.1a was used in the preparation of ethyl (β-phenylethyl) p-nitrophenyl phosphate 9.1d. This synthesis involved the addition of sodium p-nitrophenoxide to a solution of 9.1a in ether. Although the condensation did take place, the product contained up to 17% of p-nitrophenol (as determined by ^{1}H NMR spectroscopy). Since we have found (see ch. 2) that p-nitrophenyl phosphates decompose when chromatographed on silica gel, alumina (neutral) was used as the stationary phase. Elution with chloroform : pet. ether (1:1) gave pure 9.1d but with only 29% yield.

During the synthesis of bis-(β-phenylethyl) p-nitrophenyl phosphate

9.1e, and bis-[β-(p-methoxyphenyl)ethyl] p-nitrophenyl phosphate 9.1h, which were prepared by the addition of sodium p-nitrophenoxide to 9.1c and 9.1g, respectively, traces of p-nitrophenol were once again detectable in the ^{1}H NMR spectra of the crude products. We have found that washing the crude mixtures with cold, dilute aqueous sodium hydroxide, results in the effective removal of p-nitrophenol and the isolation of pure triesters with satisfactory yields.

The synthesis of diethyl (β-phenylethyl) phosphate 9.1i, was initially attempted as shown in eq. 9.3.



(9.3)

Diethylphosphorochloridate (2 mole-equivalents) in ether was added to a solution of β-phenylethanol and triethylamine (1 mole equivalent of each) in ether with stirring and cooling below 10°C. The mixture was stirred at room temperature for 1.5 h, filtered, evaporated, dissolved in chloroform and stirred with water (to remove the residual amount of the ammonium salt and the excess of phosphorochloridate) for 14 h. The chloroform solution was shown (^{1}H NMR spectroscopy) to contain a mixture (*ca.* 1:1) of the desired product and unreacted β-phenylethanol. Although column chromatography (chloroform : ethanol, 24:1) of a small sample of this mixture gave pure 9.1i (as shown by ^{1}H NMR and elemental analysis), column chromatography on a larger scale resulted in a product contaminated with triethyl phosphate (identified by ^{1}H NMR and mass spectroscopy). The latter product must have been produced by transesterification of 9.1i by

the ethanol used in the eluant. The synthesis was repeated using equimolar proportions of substrates and with pyridine as a base. After filtration, washing with water and evaporation, the liquid product was shown (^{1}H NMR spectroscopy) to consist of 9.1i (90%) and unreacted β-phenylethanol (10%). The mixture was separated by distillation, and pure 9.1i (b.p. 144°C/0.5 mm) was obtained, as shown by ^{1}H NMR and elemental analysis.

Authentic β-(p-methoxyphenyl)ethyl chloride was prepared by reduction of (p-methoxyphenyl)acetic acid[154] followed by treatment of the alcohol with concentrated hydrochloric acid in the presence of zinc chloride.[155] The final product was purified by column chromatography and obtained in 67% yield. This method of synthesis was found more favourable than that reported by Sulzbacher (final yield of *ca.* 45%).[155]

9.3 DISCUSSION

In searching for aryl participation, a simple kinetic method was employed along with product examination. The reactions were carried out by sealing the substrates in glass tubes and heating the tubes in a thermostatted water bath at 80°C. After certain time intervals, the tubes were withdrawn from the bath and cooled in dry ice/acetone before being opened. The ^{1}H NMR spectrum of the product was then recorded. The results are given in table 9.2.

In addition to examining the thermal stability of 9.1a-i, we also studied the thermal stability of ethylphosphorodichloridate 9.1j, diethylphosphorochloridate 9.1k and the chloroethane products - β-phenylchloroethane and β-(p-anisyl)chloroethane. ^{1}H NMR

Table 9.2 Decomposition of phosphate derivatives, RO-P(O)ZY at 80°C

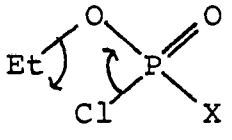
	Substrate RO	Z	Y	Reaction time (h)[a]	Conversion %	Products
9.1a	$PhCH_2CH_2O$	EtO	Cl	114	80	EtCl, $PhCH_2CH_2Cl$
9.1b	$PhCH_2CH_2O$	Cl	Cl	20	100	$PhCH_2CH_2Cl$ (minor) $(PhCHCH_2)_n$ (major)[156]
9.1c	$PhCH_2CH_2O$	$PhCH_2CH_2O$	Cl	114	90	$PhCH_2CH_2Cl$
9.1d	$PhCH_2CH_2O$	EtO	PNPO	210	0	b
9.1e	$PhCH_2CH_2O$	$PhCH_2CH_2O$	PNPO	114	0	b
9.1f	$AnCH_2CH_2O$	Cl	Cl	C	100	$AnCH_2CH_2Cl$ (minor) $(AnCHCH_2)_n$ (major)[157]
9.1g	$AnCH_2CH_2O$	$AnCH_2CH_2O$	Cl	1(2)	64(86)	$AnCH_2CH_2Cl$
9.1h	$AnCH_2CH_2O$	$AnCH_2CH_2O$	PNPO	321	0	b
9.1i	$PhCH_2CH_2O$	EtO	EtO	162	0	b
9.1j	EtO	Cl	Cl	168	0	EtCl
9.1k	EtO	EtO	Cl	162	16	EtCl

[a]The table lists the final readings; in each case the reaction mixtures were analyzed at various intervals to monitor the reaction progress.

[b]Substrate stable under these conditions.

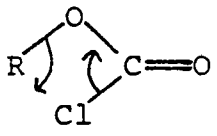
[c]Substrate decomposes at room temperature after a few hours and after one week in a refrigerator.

spectroscopy revealed that both chloroethanes were unchanged after being heated for 120 h at 80°C so justifying the monitoring of chloroethane production as a means of determining the extent of reaction. Table 9.2 records the conditions of each experiment and the obtained results. Both ethyl esters of chlorophosphoric acid (9.1j, 9.1k) were found to decompose slowly when heated at 80°C, producing chloroethane in low yields. The chloroethane was identified by ^{1}H NMR spectroscopy, after trapping the volatile reaction products in a dry/ice acetone cooled trap. The quartet at δ3.59 corresponding to the methylene protons in chloroethane was easily discernible from the reactant signals. A S_N1 type ionization of these substrates *via* C-O or P-Cl bond cleavage, producing the ethylcarbonium or phosphorylium[158] cations respectively, is unlikely because of the instability of the possible cations formed. More likely, the reaction involves direct phosphorus to carbon chloride transfer (eq. 9.4) which is possibly analogous to that which occurs during the collapse of organic chlorosulfites, chloroformates (9.5, see eq. 9.5) and thiocarbonates.[159]



$$\longrightarrow \quad EtCl + XPO_2 \qquad (9.4)$$

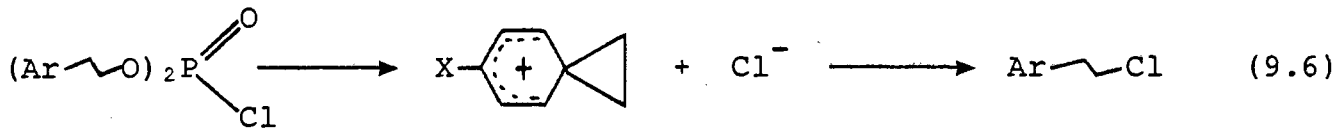
X = EtO or Cl



$$\longrightarrow \quad RCl + CO_2 \qquad (9.5)$$

9.5

However, substitution of the two ethyl groups of 9.1k by β-phenylethyl (9.1c), or even better still by β-(p-anisyl)ethyl (9.1g) substituents, results in a dramatic increase in the reactivity of the substrates. For example, after heating bis-(β-phenylethyl)-phosphorochloridate 9.1c, for 114 h at 80°C, ^{1}H NMR ($CDCl_3$) spectroscopy revealed that 90% β-phenylchloroethane was present. This was identified by comparison with the ^{1}H NMR ($CDCl_3$) spectrum of authentic β-phenylchloroethane. Fortuitously, the chemical shift of the methylene protons of the chloromethyl group in the product (δ3.58) is far enough removed from the chemical shift of the α-methylene protons in the substrate (δ4.13) for the progress of fragmentation to be determined. The rate of chloroethane production is clearly substantially enhanced by substitution of a p-methoxy group. The ^{1}H NMR ($CDCl_3$) spectrum of 9.1g recorded after only 1 h at 80°C, showed that the conversion to β-(p-anisyl)-chloroethane had reached 46%. Although the anisyl OMe signals in the product (δ3.76) and in the substrate (δ3.73) overlapped to some extent with the signals of the chloromethyl group, it was still possible to measure the reaction progress by intergration. The product was identified by addition of authentic β-(p-anisyl)-chloroethane. Undoubtedly, the rate enhancement in 9.1c and 9.1g indicates the formation of an intermediate arenium species (9.6, eq. 9.6).



(9.6)

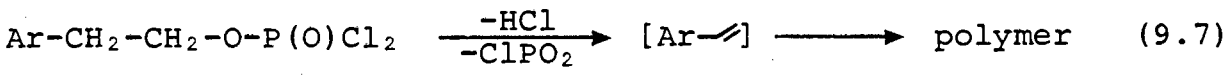
9.6

9.1c, Ar = Ph, X = H

9.1g, Ar = An, X = MeO

Introduction of a β-phenylethyl (9.1b) or β-(p-anisyl)ethyl (9.1f) substituent into the ester function of monoethylphosphorodichloridate 9.1j, also results in a substantial increase in the reactivity of the substrate. In fact the β-(p-anisyl)ethyl substituted phosphorodichloridate 9.1f was inordinately unstable and decomposed at room temperature after a few hours and after 1 week in a refrigerator. Although 9.1b was marginally more stable, it was used as soon as it was prepared.

In contrast to the mechanism of reaction of bis-(β-arylethyl)-phosphorochloridates 9.1c and 9.1g, the (β-arylethyl)phosphorodichloridates 9.1b and 9.1f offer an additional fragmentation pathway. Although the substitution products $PhCH_2CH_2Cl$ and $AnCH_2CH_2Cl$ were observed, the major reaction involves 1,2-elimination with the formation of the corresponding styrene[156,157] (eq. 9.7), the HCl formed catalysing the polymerisation.

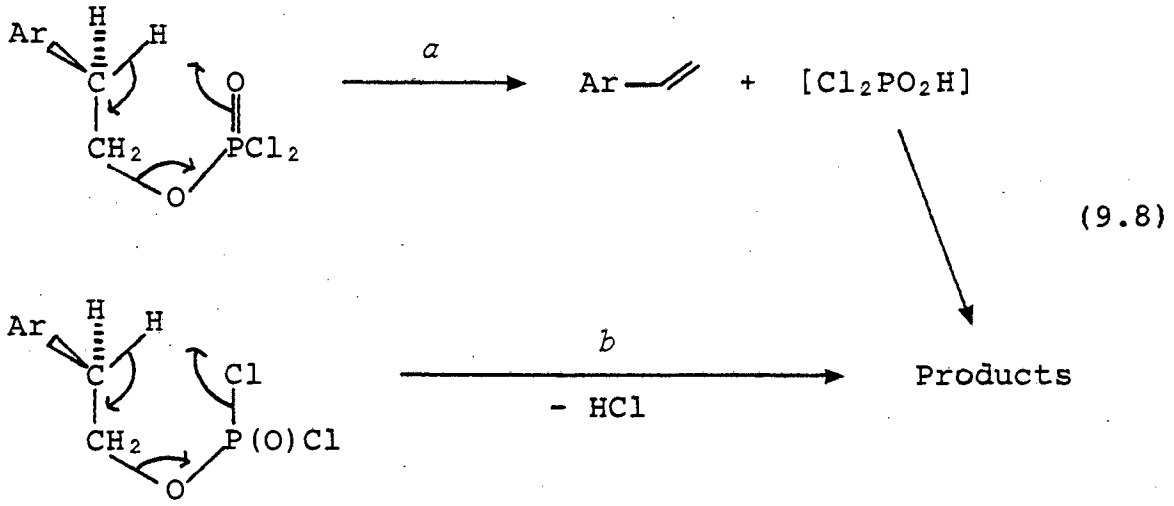


(9.7)

9.1b Ar = Ph

9.1f Ar = An

In principle, substrates 9.1c and 9.1g can also react according to eq. 9.7. However, our results provide no evidence for this pathway and it seems therefore that the preference for the elimination reaction over the nucleophilic displacement reaction is a function of the number of chlorine atoms in the substrate molecule. The enhanced reactivity of substrates 9.1b and 9.1f in the elimination reaction (relative to that of 9.1j, for which no formation of ethene was observed) results undoubtedly from the intrinsic stability of the alkene formed. Reaction 9.7 can proceed via 1,2-elimination of the corresponding phosphoric acid (eq. 9.8, pathway *a*), or it can involve fragmentation of the leaving group (eq. 9.8, pathway *b*).

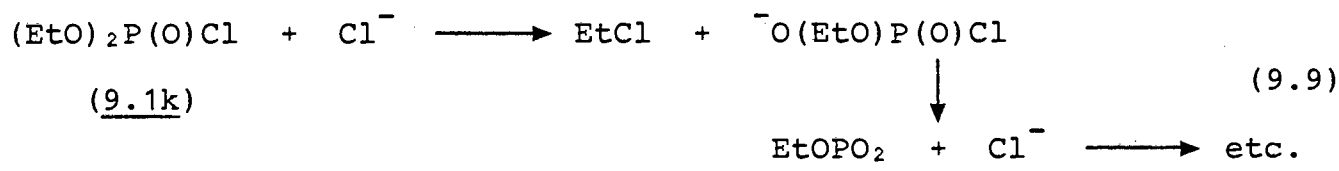


However, the triesters 9.1d, 9.1e, 9.1h and 9.1i were shown to be perfectly stable under the same conditions which provides support for pathway *b* rather than for pathway *a*. In our opinion, it is the intrinsic stability of all three fragmentation products, i.e. styrene, HCl and metaphosphate (eq. 9.8*b*) that contribute to the driving force for the elimination.

Ethyl (β-phenylethyl)phosphorochloridate 9.1a can be considered as a mixed form of the diesters 9.1k and 9.1c. The results already obtained for 9.1k and 9.1c enable us to predict that 9.1a will fragment to both chloroethane and β-phenylchloroethane. Indeed the latter product has already been identified during the distillation procedure used in the initial attempt to synthesize the substrate. We have found that, as expected, decomposition of 9.1a yields both chloroalkanes, EtCl and $PhCH_2CH_2Cl$ but in similar quantities. The molar ratio, $EtCl/PhCH_2CH_2Cl$ obtained in various experiments varied in the range 1 - 2.4. The identification of both chloroalkanes in the ^1H NMR spectrum was possible even though the triplet for the methylene protons ($-\underline{C}H_2Cl$) of β-phenylchloroethane and the quartet for the methylene protons of chloroethane overlapped partially. The presence of the former compound was proven by addition of authentic β-phenylchloroethane to the decomposition mixture.

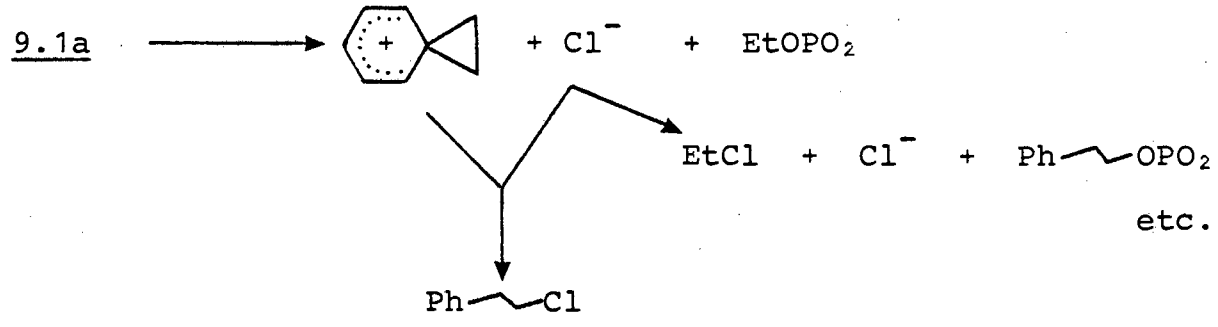
Table 9.2 shows that the reactivity of 9.1a is similar to that of 9.1c which is surprising if one also considers the results obtained for 9.1j and 9.1k. However, this result can be rationalized in the following manner. The ability of the chloride ion to displace the phosphate function at the α-carbon atom of an alkyl group is well documented,[160] and indeed, in an independent experiment which involved heating diethylphosphorochloridate 9.1k, at 80°C in the presence of 23 mole % tetraphenylphosphoniumchloride (used as a source of external chloride ions), we found that the substrate was converted into chloroethane within 64 h. This contrasts markedly with the result for 9.1k in table 9.2. Since the yield of the chloroethane formed showed complete incorporation

of all the chlorine initially present, both as ionic Cl^- (in Ph_4PCl) and as covalently bonded chlorine (in 9.1k), the external chloride acts only as a catalyst, and the reaction can be envisaged by the following sequence.



(9.9)

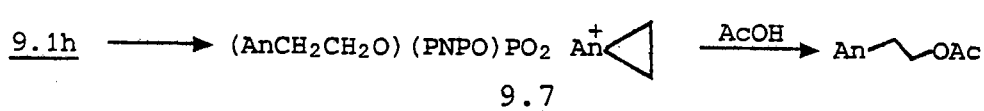
The β-phenyl substituent in the mixed diester 9.1a, plays the role of an "internal nucleophile" which releases chloride ion from the substrate molecule *via* the anchimerically assisted formation of the phenonium ion. The Cl^- ion released, can then either attack the phenonium ion to form β-phenylchloroethane - (this being the only course available for the Cl^- ion in 9.1c during the fragmentation reaction), or it can dealkylate the substrate molecule by displacing the phosphate function at the α-carbon in a manner analogous to reaction 9.9, giving chloroethane.



(9.10)

With regard to the actual mechanism of the substitution reaction, the anchimerically assisted C-O bond cleavage and the fission of the P-Cl bond (reaction 9.6) can be a synchronous or a step-wise process. Our results using substrates 9.1d, 9.1e and 9.1h in

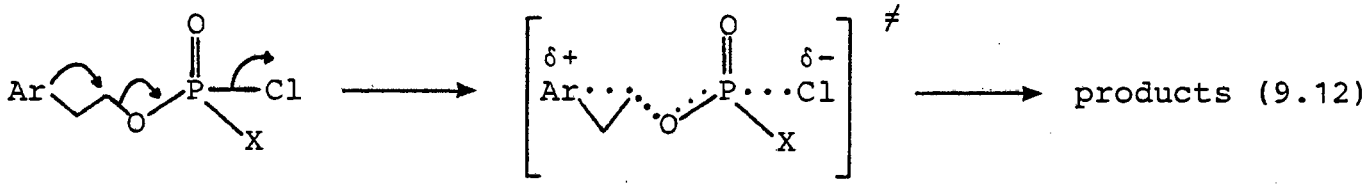
which the chlorine atom has been substituted by the p-nitrophenoxy group have helped in the elucidation of this mechanism. These substrates were found to be stable under the reaction conditions and no p-nitrophenyl (β-phenylethyl) ether (the possible decomposition product of 9.1d and 9.1e) nor p-nitrophenyl [β-(p-anisyl)-ethyl] ether (the expected product from 9.1h), were detected by means of ^{1}H NMR spectroscopy and/or TLC. Although this is in accord with the $PNPO^-$ anion being a poorer leaving group than Cl^- (the pK_a values of p-nitrophenol and HCl are 7.15[161] and -6,[162] respectively), it does not, of course, preclude the possibility of ionisation of the C-O bond of the β-arylethylphosphate function, to give the arenium ion/phosphate ion pair 9.7 (eq. 9.11). However, if this were true and the phosphate group as a whole were to behave just as a leaving group (like, for example, the arylsulfonate group), then the arenium ion formed would be easily trapped by a nucleophilic solvent. We have carried out fragmentation of 9.1h at 80°C in acetic acid as solvent monitoring the reaction by ^{1}H NMR spectroscopy and TLC. After 150 h at 80°C it was possible to determine (by ^{1}H NMR spectroscopy) that the reaction yielding [β-(p-anisyl)ethyl] acetate had proceeded to *ca.* 50%. The product was isolated by column chromatography using $CHCl_3$ as eluant and the pure product identified by ^{1}H NMR spectroscopy.



9.7 (9.11)

This result shows that the ionization of 9.1h into the corresponding arenium phosphate 9.7, is a slow process, which contrasts sharply with the rate of collapse of 9.1g with formation of the corresponding chloroalkane (reaction 9.6). This solvolysis result

together with the spontaneous collapse of the phosphorochloridate 9.1g leads us to think that reaction 9.6 does not proceed *via* fast C-O bond cleavage, followed by a slow release of the chloride ion from the phosphate ion. Rather, we believe that the following factors, i.e. the stability of the incipient ion 9.6, the departure of the chloride ion with the subsequent reorganization of the bonding at phosphorus leading to the metaphosphate-type species, are all contributing to the activation energy of the reaction. From the point of view of bonding changes at phosphorus,



the mechanism outlined in eq. 9.12 represents an analogy to that (eq. 9.8b) proposed for the elimination reaction.

In conclusion, we firmly believe that (β-arylethyl)phosphorochloridates represent a new type of organophosphorus system capable of expulsion of a metaphosphate species.* In this case, the driving

*We do not have direct evidence for the presence of the free metaphosphate species, XPO_2. The difficulties in identifying metaphosphate derivatives are well known.[150a] The trapping experiment involving phosphorylation of aromatic amines[150b] could not have been applied in the present case because of the competing reaction of aniline with the chloroalkane formed. However, in some experiments, we partitioned the reaction product between toluene and aqueous sodium hydroxide, and the ammonium molybdate test on the latter always gave strong evidence for the presence of inorganic phosphate.

force for such expulsion is the nucleophilic assistance by the aryl group with respect to the α-carbon atom, coupled together with the departure of the good leaving group (Cl^-) from the phosphoryl centre.

9.4 ELECTRON IMPACT-INDUCED FRAGMENTATION OF β-ARYLETHYL PHOSPHATES

In connection with the foregoing discussion on anchimeric assistance in β-arylethyl phosphate derivatives, we were interested to see if this study could be extended to the gas phase and whether the electron impact-induced fragmentation in the gas phase in any way paralleled the observed behaviour in the neat liquids.

With the exception of substrates 9.1f and 9.1g, all the compounds synthesized in the first part of this chapter, were submitted for mass spectral analysis. In addition, so as to obtain the relevant material for comparison, we recorded and analyzed the mass spectra of the standard compounds: diethylphosphorochloridate, 9.1k,* ethylphosphorodichloridate, 9.1j; β-phenylchloroethane and β-(p-anisyl)chloroethane. The ions from these standard compounds, which are applicable to our study are reported in Appendix IV. The ions of the substrates relevant to this study are summarized in table 9.3 (for a more complete analysis of the individual mass spectra, see experimental section).

*Although the mass spectrum of diethylphosphorochloridate has been reported in the literature,[117] it was obtained in this work so as to parallel the conditions used in our investigation.

Table 9.3 Selected mass spectral data for ß-arylethyl phosphates recorded under conditions of i 12.5 eV, T = 80-115°C or ii 70 eV, T = 200°C.

	Substrate			Molecular Ion		Base Peak	Pathway a[a]	Pathway b[a]
	RO	Z	Y			m/e		
9.1a	$PhCH_2CH_2O$	EtO	Cl	i	-	104	11[b]	24[c]
				ii	<5	104	50[b]	<2[c]
9.1b	$PhCH_2CH_2O$	Cl	Cl	i	-	104	10[b]	-
				ii	-	104	16[b]	-
9.1c	$PhCH_2CH_2O$	$PhCH_2CH_2O$	Cl	i	-	104	22[b]	<5[c]
9.1d	$PhCH_2CH_2O$	EtO	PNPO	i	<5	104	38[b]	-
				ii	<1	104	68[b]	d
9.1e	$PhCH_2CH_2O$	$PhCH_2CH_2O$	PNPO	i	<2	104	27[b]	d
9.1h	$AnCH_2CH_2O$	$AnCH_2CH_2O$	PNPO	i	-	121[e]	20[f]	g
9.1i	$PhCH_2CH_2O$	EtO	EtO	ii	<2	104	84[b]	-

[a] relative intensities (%)

[b] phenonium ion at m/e 105

[c] rearrangement product Ph—⟨⟩—Cl at m/e 140

[d] no rearrangement product Ph—⟨⟩—OPNP at m/e 243

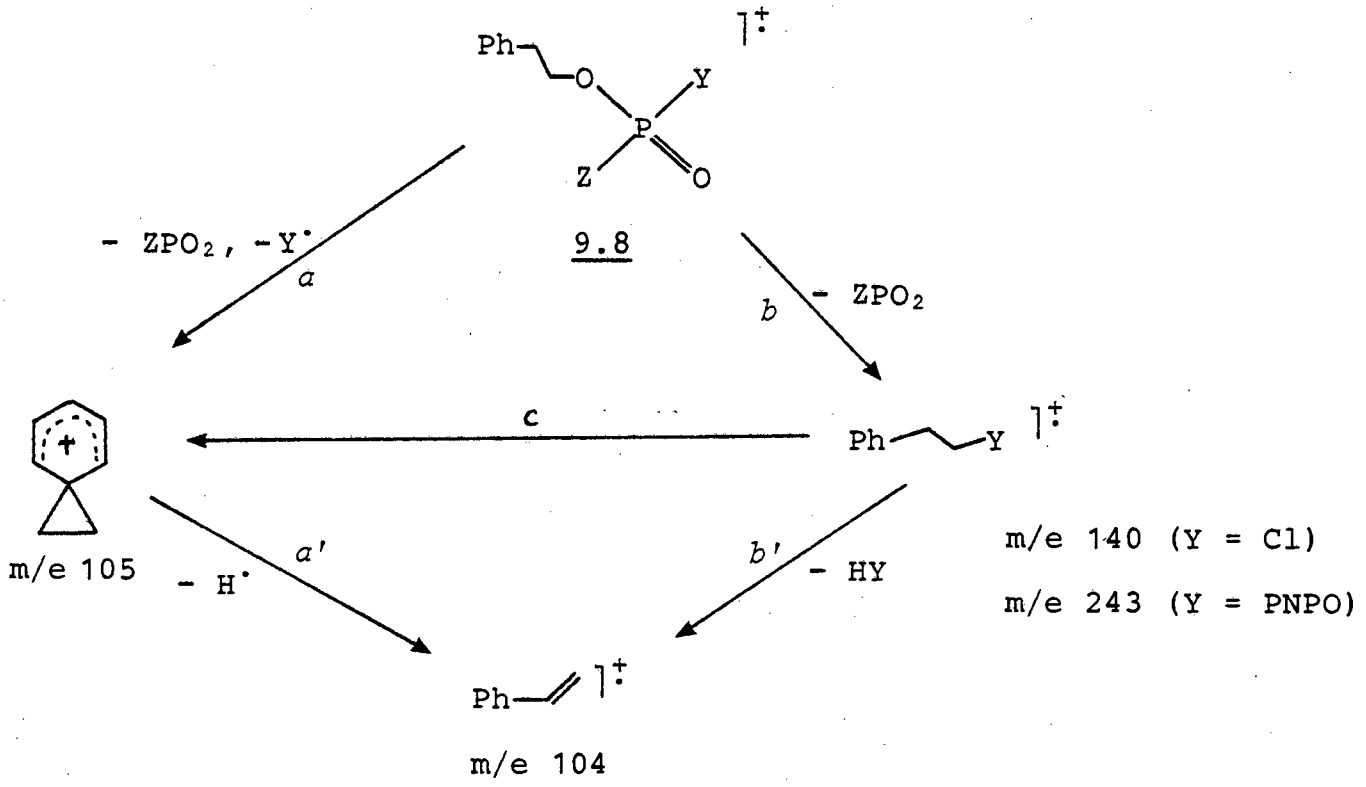
[e] base peak corresponds to p-methoxy benzyl cation but p-methoxystyrene has r.a. 86%

[f] pyridylethyleneonium ion at m/e 106

[g] no rearrangement product An—⟨⟩—OPNP at m/e 273

The first most striking feature in table 9.3 is the absence or insignificance of the molecular ions, and this immediately suggests high reactivity of β-arylethyl phosphate derivatives. From the results discussed in ch. 9.2 and 9.3, it was expected that 9.1a, 9.1b and 9.1c would exhibit high reactivity in the gas phase. The second most noticeable result from table 9.3, is that the base peak at m/e 104 is common for all the β-phenylethyl substituted substrates. This base peak corresponds to the styrene radical ion and the fragmentations which we propose for its formation are shown in scheme 9.1. These fragmentations are the most relevant to the previous discussion on the thermal behaviour of these substrates.

Scheme 9.1



Z = Ph—O, EtO, PNPO

Y = Cl, PNPO, EtO

For the general system 9.8 where Y = Cl, reaction pathway *a* can be considered analogous to the thermal reaction of 9.1a, 9.1b and 9.1c. This illustrates that the fragmentation proceeds with the synchronous expulsion of a neutral metaphosphate species, ZPO_2 and a chlorine atom to give the phenonium ion intermediate at m/e 105. This is in direct accordance with the phenonium ion mechanism proposed earlier. Table 9.3 shows that the fragment ion m/e 105, is observed with varying intensity for substrates 9.1a-e and 9.1i. Interestingly enough, this fragmentation is strongest for substrates 9.1d, 9.1e and 9.1i, i.e. phosphate esters for which no thermal fragmentation has been observed. This striking difference in fragmentation behaviour most likely results from the difference in the electronic characteristics of the fragment Y being expelled under thermal and electron impact-induced conditions respectively. In the first case, Y departs as an anion, and in the second, as a radical species. The much higher nucleofugality of the chloride ion as compared to the p-nitrophenoxide ion can be derived from the dramatic difference in the pK_a values of the corresponding conjugate acids (see pp. 297). However, in this case, nucleofugality is more closely related to the reactivity of the corresponding phosphoryl derivatives towards nucleophilic cleavage. Although rate data under identical conditions is not available, the kinetics of hydrolysis of diethylphosphorochloridate (H_2O, 30°C[164]) and diethyl p-nitrophenyl phosphate (pH 8.5, 37.5°C[165]) enable the estimation that the phosphorochloridate is at least 4×10^2-fold more reactive than the aromatic ester, to be made. On the other hand, homolytic cleavage leading to a RO$^{\cdot}$ type radical should be more favoured than the fragmentation yielding a

chlorine atom. Indeed, in the mass spectrum of 1-phenoxy-2-chloroethane the relative intensity of fragments resulting from loss of a phenoxy radical or a chlorine atom are 19 and 1.6 respectively.[166]

The phenonium ion at m/e 105, however, can also arise from a two-step fragmentation according to pathway *b* and *c*. Pathway *b* involves a rearrangement process coupled with the loss of neutral metaphosphate. A fragment ion at m/e 140 corresponding to this rearranged product β-phenylchloroethane, was observed for 9.1a and 9.1c (Y = Cl). The fact that m/e 140 was not observed for 9.1b does not necessarily imply that this fragment ion did not form. The fragmentations according to pathways *c* and *b'* to give respectively, the phenonium ion and styrene, may be so favourable as to make the appearance of the peak at m/e 140, too short-lived to be detected. No peaks at m/e 243 for 9.1d and 9.1e or at m/e 150 for 9.1c were observed, and the above reasoning can also be applied in these cases.

In the mass spectrum of β-phenylchloroethane, the molecular ion was relatively strong (r.a. 39%[a], 91%[b]) and in addition, fragment peaks at m/e 104 (r.a. 9%[a], 12%[b]) and m/e 105 (r.a. 11%[a], 34%[b]) were observed, so supporting our proposed pathways *c* and *b'*. However, loss of chlorine radical and HCl are not the dominating fragmentations. Rather, β-phenylchloroethane undergoes β-fragmentation with loss of the chloromethyl radical to form the benzyl

[a]Electron beam energy 70 eV, T = 140°C.

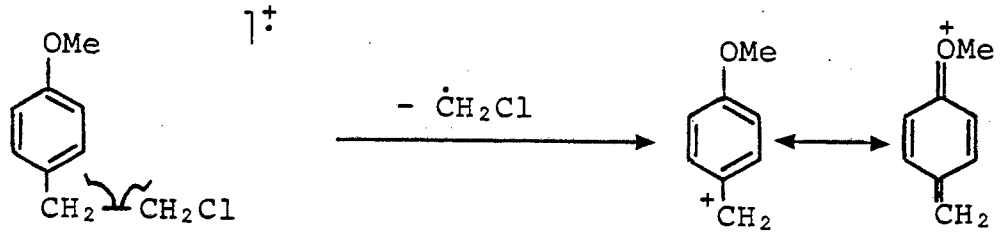
[b]Electron beam energy 70 eV, T = 100-105°C.

$C_7H_7^+$ ion (or the tropylium ion) at m/e 91 as the most abundant ion. Although this fragment ion was observed in the mass spectra of the substrates listed in table 9.3, it never dominated the spectra. We believe that this observation provides support for pathway *a* in preference to pathway *b*, further corroborating the ability of β-arylethyl phosphates 9.8, to fragment to the phenonium ion with the elimination of metaphosphate and Y·. In solution, however, the intermediate phenonium ion can recombine with chloride anion to form β-phenylchloroethane. In the gas phase, although we observe the radical ion of β-phenylchloroethane in some cases, its formation must be due to an entirely different process (see following section). Since bimolecular recombination under mass spectrometric conditions is highly unlikely, the phenonium ion loses hydrogen atom to form styrene as the most abundant ion.

In order to gain some insight into the rearrangement pathway (scheme 9.1, *b*), we recorded the mass spectrum of diethylphosphorochloridate, 9.1k. Neither a peak at m/e 64 (EtCl) nor at m/e 49 (expected from α-cleavage in EtCl[167]), was observed, indicating that the presence of the β-aryl group is essential for such a fragmentation. This may suggest that in the molecular ion 9.8, the radical cation can develop at the aromatic ring itself, thus providing the driving force for the migration of chlorine to the electron-deficient centre in the hydrocarbon moiety. Such an effect is, of course, not possible for the ethyl ester group in 9.1k.

Although the mass spectrum of bis-[β-(p-anisyl)ethyl] p-nitrophenyl phosphate 9.1h, shows fragmentations corresponding to the major fragmentations of its phenyl analogue 9.1e, the spectrum is, as

expected, influenced by the presence of the p-methoxy group. In common with the other β-arylethyl phosphate esters, no molecular ion was observed. Although the principle ions in the mass spectrum of anisole are derived from initial cleavages at the methoxyl function,[168] neither was a M - $CH_3^{\cdot}$ fragment observed in the mass spectrum of β-(p-anisyl)chloroethane. The spectrum of the latter was, however, relatively simple, consisting of the molecular ion at m/e 170 (r.a. 21%) and the base peak at m/e 121 dominating the spectrum. Failure to observe loss of methyl radical from the molecular ion can be attributed to β fragmentation with loss of chloromethyl radical and formation of the resonance stabilized benzyl cation 9.9.



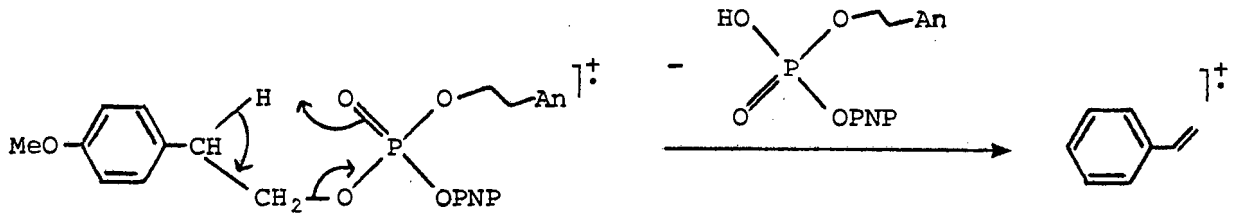
(9.13)

9.9

Evidence for the loss of chlorine atom or 1,2-elimination with loss of HCl was minimal. The fragmentation patterns of β-(p-anisyl)- and β-phenylchloroethane were therefore found to be very similar.

Similarly, in the mass spectrum of 9.1h, the base peak also appeared at m/e 121 and could be assigned to the resonance stabilized benzyl cation 9.9. However, the fragment ions at m/e 134 (r.a. 82%) corresponding to β-(p-methoxystyrene) radical ion and at m/e 135 (r.a. 21%) for the p-methoxyphenonium ion were evidence that elimination is also an important fragmentation pathway. Equation

9.12 shows elimination of a phosphoric acid derivative *via* a 6-membered ring to give m/e 134 directly.

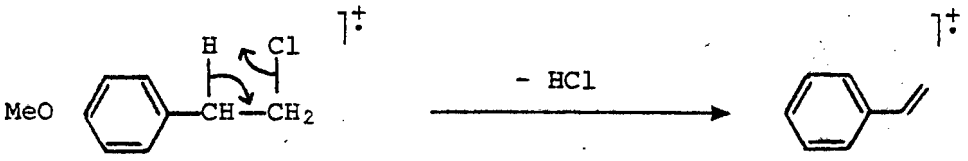


(9.14)

m/e 134

(r.a. 82%)

The very low intensity ion at m/e 134 (r.a. <1%) in the mass spectrum of β-(p-anisyl)chloroethane is postulated as forming by a much less favourable elimination reaction *via* a 4-membered ring.

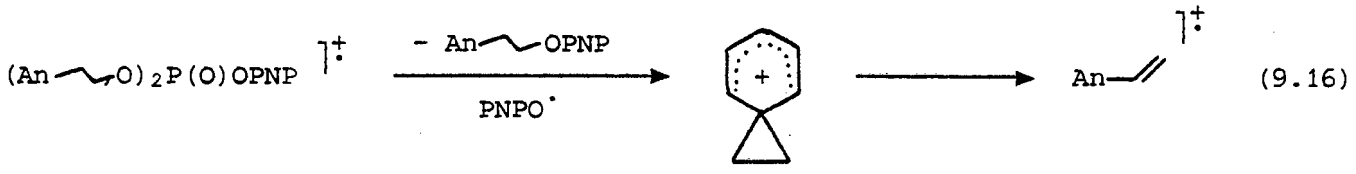


(9.15)

m/e 134

(r.a. < 1%)

Elimination from 9.1h can also occur according to pathway *a* and *a'* in scheme 9.1 and this would account for the peak at m/e 135 (eq. 9.16).



(9.16)

m/e 135

(r.a. 21%)

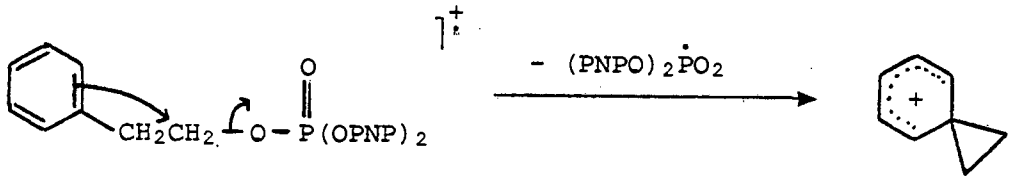
As before, the observed difference in the effectiveness of the anchimeric assistance observed for 9.1h in the mass spectrum (formation of ion m/e 135) and under thermal conditions (as demonstrated by slow acetolysis of 9.1h, see pp. 297) can be explained

in terms of the ionic versus radical nature of one of the reaction products.

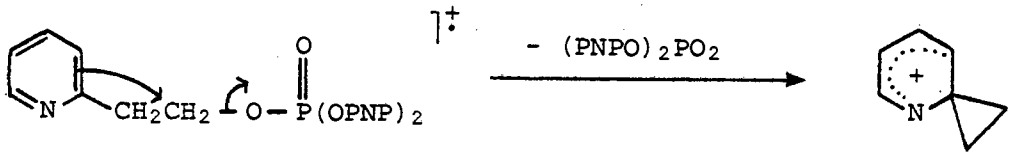
We have already partly discussed the mass spectra of bis-(p-nitrophenyl)(β-pyridylethyl) phosphate (2.1c) and bis-(p-nitrophenyl)-(β-phenylethyl) phosphate (2.1d) in ch. 2. At that time our discussion was focused primarily on the $M^{+\cdot}$ - PNPO$^{\cdot}$ fragmentation which was relevant to the particular hydrolysis studies in solution. However, it is now pertinent to consider the formation of the pyridylethyleneonium and phenylethyleneonium (phenonium) ions for substrates 2.1c and 2.1d, respectively.

In the mass spectrum of 2.1d, the fragment ion at m/e 105 i.e. the phenonium ion 9.10, had a relative intensity of *ca*. 78%. The corresponding pyridylethyleneonium ion 9.11 at m/e 106 in the mass spectrum of 2.1c, however, was of minor importance having a relative intensity of only *ca*. 9%. Both these fragment ions can be postulated as forming with general aryl group participation, with γ* bond cleavage and expulsion of bis-(p-nitrophenyl) phosphoryloxy radical as shown in eq.s 9.17 and 9.18. The observed difference in the abundance of ions 9.10 and 9.11 results certainly from the destabilizing effect of nitrogen upon the carbonium ion formed. The low intensity of the ion 9.11 negates also any direct participation of the nitrogen atom in the fragmentation; such assistance would have led to a highly strained, 4-membered cyclic 1,2-pyridinium cation.

*See ch. 7 footnote pp. 238

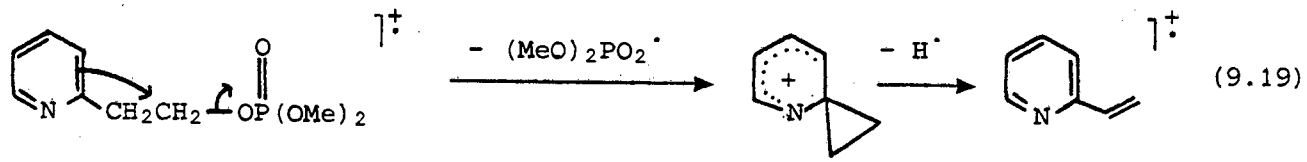


2.1d 9.10



2.1c 9.11

In ch. 7, the mass spectrum of dimethyl-[β-(2-pyridylethyl)] phosphate B was discussed and we have proposed that the base peak at m/e 105 results from an elimination reaction following the McLafferty rearrangement (see eq. 7.5). However, the evidence for aryl participation and γ bond cleavage as shown in eq. 9.19 is by no means trivial as the peak at m/e 106 corresponding to spiro pyridinonium type ion 9.11, is the third most abundant peak in the spectrum (relative intensity = 64%). Loss of H· from 9.11 will also result in the resonance stabilized alkene at m/e 105.



m/e 106 m/e 105

B 9.11

We have also proposed that the spiro-type ion 9.11 exists in the mass spectrum of [β-(2-pyridylethyl)] acetate, F (see ch. 7.6.2). However, no mention was made of the acylium ion at m/e 43 resulting from δ bond cleavage (see footnote a on pp. 238). Turning now to this, we find that the fragment ion at m/e 43 is present, although its relative intensity varied from 92% - 25% in two separate samples* (the peak at m/e 106 underwent a corresponding variation in r.a. of 50 - 20%). It is of interest to compare this result with data from the spectra of additional acetates and so determine whether MeC(O)-O bond cleavage with acylium ion formation is always a more favourable fragmentation than MeC(O)-R fragmentation. The results of a literature study of a series of alkyl esters together with our own observation are given in table 9.4. It appears that the stability of the anticipated cation formed by γ bond cleavage is important in determining the relative abundance of the $M - Me\dot{C}O_2$ fragment ion. For example, in t-butyl acetate the $M - Me\dot{C}O_2$ peak has a r.a. = 50% compared with 4.5% for n-butyl acetate. Even more pertinent is the direct comparison between [β-(2-pyridylethyl)] acetate and β-phenylethyl acetate. Although the m/e 43 fragment ion features strongly in the spectra for both compounds, it does not dominate the spectra. The McLafferty rearrangement involving loss of acetic acid gives rise to the base peak in the spectrum of β-phenylethyl acetate.

Equation 7.24 shows the analogous rearrangement for [β-(2-pyridylethyl)] acetate but for the pyridyl derivative, this fragment ion had an intensity of only 20% for the base peak (protonated 2-pyridylethanal).

*70 eV: T = 200°C, r.a. 92%; T = 100-105°C, r.a. 25%.

Table 9.4 Comparison of $Me\overset{+}{C}=O$ formation and $Me\dot{C}O_2$ expulsion in the mass spectra of selected acetates.[a]

Substrate	Ion observed[b] $Me\overset{+}{C}=O$, m/e 43	M - $Me\dot{C}O_2$
[β-(2-pyridylethyl)] acetate[c]	92(25)	50(20)
ethyl acetate	100	22
t-butyl acetate	100	50
isoamyl acetate	100	5
n-butyl acetate	100	4.5
n-amyl acetate	100	4.8
2-methylbutyl acetate	100	5.0
2-ethoxyethyl acetate	100	3.3
3-chloropropyl acetate	100	1.2
β-phenylethyl acetate[d]	82	12.8

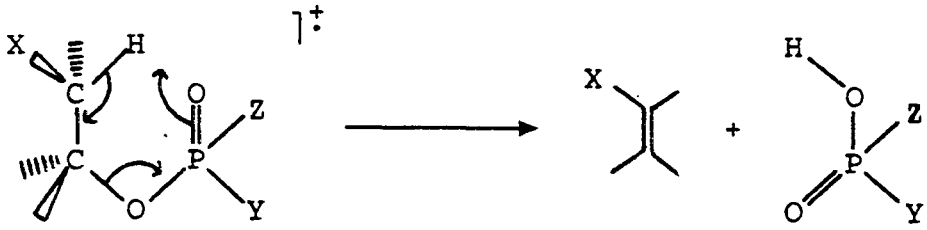
[a]With the exception of F, data obtained from ref. 169.

[b]Relative intensities (%).

[c]Mass spectra recorded at 70 eV, T = 200°C; figure in parenthesis refers to T = 100-105°C.

[d]Base peak at m/e 104 corresponds to styrene.

So far we have been primarily concerned with processes which cannot be accounted for by simple bond cleavages and for which aryl-participation mechanisms are therefore possible. This does not imply the unequivocal aryl participation in the gas phase, but it is certainly consistent with the formation of spiro ions 9.10 and 9.11. The following generalizations as well as specific observations are noted from the mass spectra of this class (β-arylethyl phosphates) of compounds. Firstly, the McLafferty rearrangement (eq. 9.20), a single hydrogen shift operating for ions (or radical ions) capable of electronic shift involving a 6-membered cyclic molecular framework, is not a favourable fragmentation pathway for this class of compounds - the fragment ions corresponding to this rearrangement, if present, having a relative intensity of less than 6%.



(9.20)

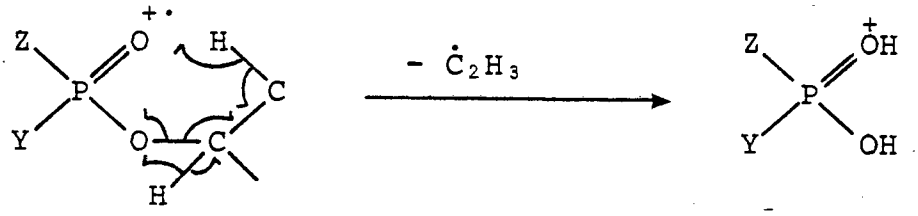
X = H, Ph, An

Y = Cl, EtO, Ph—O, An—O

Z = Cl, EtO, PNPO

Loss of ethylene (M - 28) was not observed for diethylphosphorochloridate 9.1k and this observation is in accord with Pritchard's[117] result. Similarly, loss of ethylene from the parent ion has not been reported in the mass spectrum of triethyl phosphate.[106] A M - 28 peak, albeit 6%, was, however, observed in the mass spectrum

of ethylphosphorodichloridate 9.1j. Rather, in the case of the ethyl esters, 9.1a, 9.1d, 9.1j and 9.1k, loss of vinyl radical ($\dot{C}_2H_2$) from daughter or molecular ions is more favoured. The mechanism involves a double hydrogen shift involving the abstraction of one α- and one β-hydrogen atom from the ethoxy group.



(9.21)

Z = Ph—O, EtO, Cl

Y = Cl, PNPO

With exception of 9.1i, there was no evidence for the analogous hydrogen rearrangement involving loss of the β-styryl radical PhCH=$\dot{C}$H, or the β-(p-methoxystyryl) radical MeO-C_6H_4CH=$\dot{C}$H. Although the mass spectrum of diethyl(β-phenylethyl) phosphate 9.1i showed a a peak corresponding to a M - Ph—// species (r.a. = 5%), it also showed a peak for the M - Ph—// species (McLafferty rearrangement, r.a. 3%). However, neither hydrogen shifts were prominent.

Although the thermal dependence of formation of tetraalkyl pyrophosphates from various organophosphorus precursors has recently been discussed,[170] we have recorded the spectrum of 9.1k not only at the standard temperature and electron beam energy (210°C, 70 eV), but also at 105-150°C/70 eV and at low temperature and low electron beam energy (95-130°C/12.5 eV). Our results are given in table 9.5 and suggest that it is not necessarily only the temperature of the ion-source, nor the electron beam energy which dictate pyrophosphate formation, but rather the length of time on the ion-source prior to detection.

Table 9.5 Tetraethyl pyrophosphate formation as a function of mass spectrometric conditions.

Temperature (°C)	Electron Beam Energy (eV)	Scan Time (min)	$[(EtO)_2P(O)]_2$ (r.a. in %)
210	70	0.13	-
		0.22	10
105→150	70	0.35	21
		1.43	24
95→130	12.5	1.25	100

There was no evidence for tetraethyl pyrophosphate or the mixed anhydride in the mass spectrum of diethyl (β-phenylethyl) phosphate 9.1i which supports the proposed mechanism of pyrophosphate formation in dialkylphosphorochloridates as involving initial hydrolysis to the corresponding acid, followed by thermal dehydration. Interestingly, no pyrophosphate was present in the mass spectrum of ethyl (β-phenylethyl)phosphorochloridate, 9.1a.

An additional common feature in the mass spectra of the 9.1b, 9.1g as well as in the spectra of β-(phenylchloroethane) and β-(p-anisylchloroethane), is the presence of peaks at m/e values greater than those of the corresponding molecular ions. These peaks are accompanied by further peaks, evidently derived from these high mass ions and being multiples primarily of 104 m/e units. Fortunately, this polymerization occurred after the first scan had been obtained so enabling the 'primary fragmentations' to be observed (for clarity purposes, these peaks are not listed in the experimental section).

Finally, in connection with the discussion in ch. 2, regarding the mass spectra of bis-(p-nitrophenyl) phosphate derivatives, we looked in particular at the mass spectra of 9.1d, 9.1e and 9.1h for peaks corresponding to loss of the p-nitrophenoxy radical $(M - 138)^+$ or to formation of the p-nitrophenol radical ion. Loss of PNPO$^\cdot$ did not occur, presumably because phosphorylium ions $(RO)_2P(O)^+$ are generally considered as unstable species[158] (although the M - PNPO$^\cdot$ fragment ion was the base peak in the spectrum of 2.1e, the electron-deficient phosphoryl centre could be resonance stabilized by interaction with the quinolyl nitrogen). The PNPOH fragment ion did, however, appear in the spectra of these compounds, but it was of minor importance.

Chapter 10

Conclusion

CONCLUSION

The aim of this project was to investigate the chemistry of selected phosphate esters which serve as good models for a study of the effects of structural modifications on the reactivity of the "energy rich" phosphate bond and/or the carbon-oxygen bond of a phosphate ester.

The choice of phosphate triester substrates for studies in solution (alkaline hydrolysis) and in the gas phase (electron impact-induced fragmentation), has enabled us to probe the proximity effect of a heterocyclic atom (pyridyl or quinolyl nitrogen) relative to reference substrates (the carbocyclic analogues). As expected, the heterocyclic derivatives showed an increased susceptibility of the phosphoryl centre to hydrolysis. This was considered in the light of both the intrinsic nucleophilicity of the nitrogen atom and its inductive effect. For the pyridyl containing compounds, no conclusive evidence for neighbouring participation (intramolecular general base or nucleophilic catalysis) was found and the observed rate enhancement relative to the carbocyclic analogues results most likely from the polar effects of the pyridyl group. For the quinolyl derivative, in which the geometrical constraint limits the number of rotational degrees of freedom, we believe that the intramolecular catalytic effect exists. For the pyridyl and quinolyl phosphate esters, positive indication for intramolecular interaction of the heteroaromatic ring with phosphorus was found under conditions of electron impact-induced fragmentation.

The attempts to develop procedures for the synthesis of mixed

triesters of phosphoric acid containing a heterocyclic atom in one of the ester groups were met by a number of difficulties. This was because of the potential number of reactive centres within one molecular framework. Particularly when the target compound was designed to contain a methyl ester substituent, the participation of the heterocyclic atom and/or the external base in demethylation reactions was prevalent.

The alkylating properties of the methyl phosphate ester group were investigated in more detail (ch.s 4 and 5). Both qualitative and quantitative studies indicated high reactivity and solvent dependence of the methyl phosphates in the presence of nitrogen nucleophiles. In the case of the isomerisation of a bifunctional substrate to its zwitterionic product, no kinetic evidence was found for the intramolecular methyl transfer - the reaction proceeds *via* bimolecular nucleophilic displacement with the formation of ionic intermediates.

We have shown that an apparently simple triester, dimethyl-(quinolin-8-yl) phosphate (C) when dissolved in water presents a highly reactive system involving such reactions as: methanol formation (probably *via* the attack of water at the methyl group); release of 8-hydroxyquinoline (nucleophilic cleavage of the P-OAr bond); and methyl transfer from oxygen → nitrogen (most likely an intermolecular mechanism). Most of the products thus formed can undergo numerous subsequent reactions so a quantitative description of this system was not possible. It would be interesting to study this reaction by high resolution ^{31}P NMR spectroscopy in order to monitor the formation and decay of all phosphorus-containing species.

Unfortunately, when this project was carried out, we were not in possession of adequate instrumentation for this purpose. The bimolecular nature of the O→N methyl group transfer in dimethyl-(quinolin-8-yl) phosphate (C) was supported by the intermolecular relations of the functional groups in the solid state. This correlation can serve as another illustration of the approach according to which crystal structures can serve as models for species occurring along the reaction coordinate.

Medium effects on the methyl transfer reaction were studied using a simple system involving trimethyl phosphate and pyridyl nucleophiles. Water was found to be the most suitable medium for this process and we interpret this result in terms of the progressively increasing affinity towards water in the series phosphate triester, diester, monoester and inorganic phosphate. These results can be related to the crystallographic study on hydrogen bonding in phosphates, carried out in our laboratory. It would be interesting to extend this kinetic study to a direct comparison between the methylating properties of trimethyl phosphate and other methylating agents (halomethanes, methyl tosylates, etc.), and of solvent effects on these properties.

We have found the results described in ch. 9 particularly rewarding. The discovery of β-aryl group participation in the phosphate system is a novelty in itself. The fact that this fragmentation involves the expulsion of a metaphosphate species under mild conditions contributes, we believe, to the general study of the role of metaphosphate intermediates in phosphorus chemistry. By virtue of product analysis, we were able to point out that product formation

(substitution versus elimination) is a sensitive function of the detailed structure of the substrates. This provides a starting point for a comprehensive study on the structure reactivity relationships and mechanisms of collapse of simple phosphoryl derivatives.

Chapter 11

Experimental

11.1 GENERAL

^{1}H NMR spectra were recorded on a 60 MHz Varian EM 360A and on a 100 MHz Varian XL100 spectrometer with tetramethyl silane (TMS) or with the sodium salt of 3(trimethylsilyl)-propanesulfonic acid (DSS) as an internal reference. ^{13}C NMR and ^{31}P NMR were recorded on a Bruker WH90 spectrometer operating in the FT mode. IR spectra were recorded on a Perkin Elmer 180 spectrophotometer. Mass spectra were recorded on a VG Micromass 16F spectrometer. Melting points (uncorrected) were determined with a Fischer-Johns m.p. apparatus. Analyses for C, H and N were performed at the University of Cape Town using a Heraeus Universal combustion analyser. Alkaline hydrolysis kinetics were carried out in a quartz cell in the thermostatted cell compartment of a Beckman 5260 spectrophotometer. Water at constant temperature (25 ± 0.2°C) was circulated through the sample cell by use of a Haake constant temperature circulator. Unless otherwise stated, aluminium-backed silica gel plates (Merck, Kiesegel 60 F_{254}, Art. 5554) were used for TLC and 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). Aluminium oxide (Merck, 90 active, neutral, Art. 1077, 70-230 mesh ASTM) and aluminium-backed aluminium oxide plates (Merck, 60 F_{254} neutral (type E), Art. 5550) were used in one instance for column chromatography.

Reverse phase column chromatography was carried out on silica gel[172] columns using Whatman TLC plates.

11.2 REAGENTS

The following reagents were used as supplied: diphosphorus pentoxide, magnesium sulphate, 4-methoxyphenyl acetic acid, 4-(dimethylamino) pyridine, sodium acetate, 1-fluoro-4-nitrobenzene, tetraphenylphosphonium chloride, zinc chloride (Merck); sodium hydroxide, sodium chloride (Laboratory and Scientific Equipment); sodium metal, p-methoxystyrol, styrene δ_6-acetone, δ_3-acetonitrile, δ_6-dimethylsulfoxide, δ-chloroform, δ_3-methanol and deuterium oxide (Aldrich Gold Label); iodomethane,* sodium hydroxide and hydrochloric acid volumetric ampoules (B.D.H.).

AnalaR acetone, acetonitrile, benzene, carbon tetrachloride, chloroform, dichloromethane, diethyl ether, ethyl acetate isopropanol, nitromethane, petroleum ether, tetrahydrofuran and toluene were used after drying according to standard procedures.

Benzyl alcohol, 2-pyridylmethanol, β-phenylethanol, β-(2-pyridyl)-ethanol, β-phenylchloroethane, phosphorus trichloride, phosphorus oxychloride, phenyl phosphorodichloridate, trimethyl phosphate, triethyl phosphate, pyridine sulphuryl chloride, 4-nitrophenyl phosphorodichloridate (Merck); triethylamine (Hopkin and Williams), 2,6-lutidine, diethyl phosphorochloridate, dimethyl sulphate,* methyl trifluoromethanesulfonate* (Aldrich Gold Label); acetic anhydride nitromethane and phenol (B.D.H.) were distilled before use. All water was glass distilled.

*Handled as a possible carcinogen because of its alkylating properties.

8-hydroxyquinoline (Merck) was purified by recrystallization from ethanol:water (2:1).

Nitrogen, when used as an inert atmosphere was dried by passing through concentrated sulphuric acid, and then further dried over P_4O_{10}.

Dry nitric acid was prepared by adding 40 cm^3 (0.75 mol) concentrated sulphuric acid dropwise to 25 cm^3 (0.595 mol) fuming nitric acid. The mixture was distilled and the clear yellow fraction of nitric acid collected, b.p. 92-94°C (760 mm).

4-nitrophenol (B.D.H.) was purified by recrystallization from benzene (m.p. 112-114°C).

4-pyridylmethanol (Merck) was purified by distillation, b.p. 120°C/0.2 mm and then further by recrystallization from benzene (50%). m.p. 58-61°C (lit.[43] 57.8-58.8°).

'Super-dry'[173] methanol (AnalaR) was prepared by refluxing a mixture of 1 g dry magnesium turnings (B.D.H.), 0.1 g iodine (Merck) and 20 ml MeOH for 1.5 h in a 250 ml round bottom flask. An additional 170 ml MeOH was added and the mixture refluxed for a further 2 h. The methanol was distilled, b.p. 64°C onto type 4 Å molecular sieves.

Sodium hydride (Merck) was supplied as a dispersion (80%) in paraffin oil. The oil was removed prior to the reaction by washing the dispersion with toluene (dried over pressed Na) at least 4 times. After decanting the solvent, containing the oil, the NaH was immediately covered with a fresh aliquot of solvent.

Sodium methoxide was prepared by adding 0.27 g metallic Na to 30 ml 'super-dry' MeOH in a round bottom flask with cooling and with exclusion of moisture. After complete dissolution, MeOH was removed under reduced pressure to give a white solid which was immediately covered with pet. ether.

Methylphosphorodichloridate. 13.6 ml MeOH was added dropwise to a solution of $POCl_3$ (0.336 mol) in ether (60 ml) at 0°C. The mixture was stirred for 2 h and the ether and HCl removed under reduced pressure. The crude product was purified by distillation to give $MeOP(O)Cl_2$ (79%), b.p. 62-66°C/15 mm.

Sodium p-nitrophenoxide. 10 g p-nitrophenol (0.072 mol) was dissolved in a minimum volume of ether. To this was added 2.9 g NaOH dissolved in 5 ml water. The solid product which precipitated during the addition was collected by filtration. The remainder of the product was obtained by removing the solvent under reduced pressure. The salt was heated in an over at 80°C for 3 h prior to use.

Ethylphosphorodichloridate. This was prepared from EtOH and $POCl_3$ according to the procedure described for methylphosphorodichloridate. The crude product was distilled under reduced pressure. 77% yield, b.p. 66-68°C/15 mm.

p-Nitrophenylphosphorodichloridate.[174] 53 ml $POCl_3$ (0.574 mol) was refluxed with 13.3 g PNPOH (0.096 mol) and 0.32 g NaCl. The synthesis was monitored by ^1H NMR spectroscopy and the reaction was complete after 11 h. The excess $POCl_3$ was removed under reduced pressure once HCl evolution had ceased. 86% yield. The product was used without further purification.

Sodium dimethyl phosphate.[87] A solution containing 4 g NaOH pellets dissolved in 50 ml 80% aqueous ethanol was added to $(MeO)_3PO$ (14 g). The mixture was left stirring for 4 h at room temperature and the solvents then removed under reduced pressure. The white residue was washed with ether and dried in a dessicator. Yield 80%. ^1H NMR (D_2O): δ 3.59 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3).

Dimethylphosphorochloridate.[175] A solution of 44 ml freshly distilled PCl_3 in 44 ml dry benzene was added dropwise over 1 h to a cold, stirred solution of 61 ml dry MeOH in 150 ml dry benzene. The temperature of the reaction solution was maintained at 5-10°C throughout the addition. Freshly distilled SO_2Cl_2 (41 ml) was then added dropwise to the mixture which was left standing overnight. The volatile products and solvent were removed under reduced pressure and the crude product was purified by distillation at 92°C/20 mm (lit.[175] b.p. 55-57°C/2-3 mm). 79% yield.

11.3 SUBSTRATES

Bis-(p-nitrophenyl)-phosphorochloridate.[15] Diphenylphosphorochloridate (12.7 ml, 0.0615 mol) in a 3-necked flask equipped with a magnetic stirrer, thermometer, dropping funnel and drying tubes was dissolved in 25 ml dry CCl_4. A mixture consisting of 27% anhydrous HNO_3 plus 73% H_2SO_4 (24.5 ml) was added dropwise at a rate which permitted keeping the reaction mixture at 5-12°C. After 4 h of stirring at 10-12°C, the reaction mixture was extracted with 5 x 50 ml aliquots CH_2Cl_2 with the exclusion of moisture. This mixture was then neutralized by stirring with anhydrous Na_2CO_3. The orange precipitate was filtered by gravity filtration and the solvent removed under reduced pressure on a rotary evaporator leaving a cream coloured residue. 92% yield, m.p. 93-95°C (lit.[15] 97-97.6°C). (Found: C, 40.2; H, 2.55; N, 7.8%. $C_{12}H_8O_7ClN_2P$ requires C, 40.19; H, 2.25; N, 7.81%).

Bis-(p-nitrophenyl) (β-phenylethyl) phosphate, 2.1d 0.0102 mol bis-(p-nitrophenyl)-phosphorochloridate, in a 3-necked flask equipped with a magnetic stirrer, thermometer, dropping funnel and drying tubes, was dissolved in 20 ml dry benzene. A mixture of β-phenylethanol (0.0102 mol) and dry pyridine (0.0106 mol) in 10 ml benzene was added dropwise at a rate which permitted keeping the reaction mixture at 10-12°C. After stirring for 20 h at room temperature, the white precipitate of the pyridinium chloride was removed by filtration. Evaporation of solvent under high pressure (0.2 mm) gave a yellow/orange oil which solidified upon standing. Yield 89%. The crude product was purified by column chromatography eluting with acetone:chloroform (7:3). Overall yield, 83%, m.p. 72-75°C. ^{1}H NMR ($CDCl_3$): δ 3.07 (2H, t, $J_{H,H}$7Hz, βCH_2); 4.58 (2H, q, $J_{H,H}=J_{H,P}$7Hz, αCH_2); 7.18-7.40 (9H, m, C_6H_5 and 4 protons *meta* to NO_2); 8.23 (4H, d, J_{ortho}9Hz, protons *ortho* to NO_2). MS: m/e 306 (M^+) (Found: C, 53.95; H, 3.9; N, 6.3%. $C_{20}H_{17}O_8N_2P$ requires C, 54.06; H, 3.86; N, 6.30%).

Bis-(p-nitrophenyl) [β-(2-pyridylethyl)] phosphate, 2.1c. The phosphorylation reaction was carried out in a 3-necked flask equipped with a magnetic stirrer, thermometer, dropping funnel and drying tubes. Triethylamine (0.6 ml) was added to β-(2-pyridyl)-ethanol (0.47 ml) in benzene (10 ml). 1.5 g bis-(p-nitrophenyl)-phosphorochloridate (4.2×10^{-3} mol) in 10 ml benzene was then added at a rate which maintained the temperature at ≤ 10°C. This addition took 1 h. The mixture was left to stir at ≤ 10°C for a further 1.5 h. After standing overnight at room temperature, the white precipitate was removed by filtration and thoroughly washed with benzene. The combined benzene solution was removed on a

rotary evaporator leaving cream coloured crystals which were recrystallized from benzene/pet. ether. 94% yield, m.p. 100-102°C. ^{1}H NMR ($CDCl_3$): δ 3.20 (2H, t, $J_{H,H}$7Hz, βCH_2); 4.75 (2H, q, $J_{H,H}=J_{H,P}$7Hz, αCH_2); 6.90-7.62 (7H, m, 4 protons *meta* to NO_2 and 3 pyridyl protons); 8.10 (4H, d, J_{ortho}9Hz, protons *ortho* to NO_2); 8.45 (1H, d of d, J_{ortho}5Hz, J_{meta}2Hz, proton *ortho* to pyridyl N). MS: m/e 307 (M^+) (Found: C, 51.25; H, 3.65; N, 9.35%. $C_{19}H_{16}O_8N_3P$ requires C, 51.25; H, 3.62; N, 9.44%).

The attempted synthesis of the following mixed triesters of phosphoric acid has been described in ch. 2.5: methyl (p-nitrophenyl) (β-phenylethyl) phosphate, 2.13a; ethyl (p-nitrophenyl) (β-phenylethyl) phosphate, 2.13b; and phenyl (p-nitrophenyl) [β-(2-pyridylethyl)] phosphate 2.13c. The reaction between sodium methoxide and bis-(p-nitrophenyl) β-phenylethyl phosphate, 2.1d, has also been described.

General experimental procedure for the preparation of selected dimethylaryl and dimethyl(arylalkyl) phosphates

Substrates A, B, C and D were prepared according to the "alkoxide" method which entailed the following: NaH (*ca.* 0.08 mol) was placed in a 3-necked round bottom flask which was protected from moisture at all times, and washed as described earlier with toluene.* The alcohol or phenol (*ca.* 0.045 mol) was dissolved in 40 ml toluene and added dropwise to the NaH suspension with stirring. There was a slight heat effect and the mixture was stirred at room temperature for 2 h while H_2 gas evolved. A second 3-necked flask was fitted with a dropping funnel, low-temperature thermometer and drying tube. $(MeO)_2P(O)Cl$ (*ca.* 0.045 mol) in 40 ml dry ether was

* The reaction was carried out under an atmosphere of dry nitrogen.

placed in the flask. The sodium salt was siphoned under a positive N_2 pressure from the slight excess of NaH used in its preparation, which was washed with 3 x 15 ml aliquots toluene, and the combined toluene solution added dropwise to the ice-salt bath cooled solution of $(MeO)_2P(O)Cl$ with stirring. The temperature was kept below 8°C throughout the addition. The reaction mixture was subsequently stirred for at least 3 h at room temperature. NaCl was separated by gravimetric filtration or centrifugation (the latter was found to be more effective) washing well with dry ether. The solvents were removed from the filtrate under reduced pressure to yield the crude product. See following text for purification procedures of A, B, C and D.

Dimethyl-(2-pyridylmethyl) phosphate, A. A was prepared according to the "alkoxide" method and the crude product (a red oil) was purified by column chromatography, eluting with chloroform:ethanol (4:1). r.f. A = 0.89. 79% yield. ^1H NMR ($CDCl_3$): δ 3.83 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3); 5.25 (2H, d, $J_{H,P}$9Hz, αCH_2); 7.20-8.08 (3H, m, protons *meta* and *para* to pyridyl nitrogen); δ 8.70 (1H, d, J_{ortho}5Hz, proton *ortho* to pyridyl nitrogen); MS: m/e 217 (M^+). (Found: C, 44.40; H, 5.60; N, 6.55%. $C_8H_{12}O_4PN$ requires C, 44.25; H, 5.57; N, 6.45%).

Dimethyl-[β-(2-pyridylethyl)] phosphate, B. The "alkoxide" procedure was followed and resulted in pale yellow oil. B was purified by column chromatography using chloroform:ethanol (4:1) as the eluant. r.f. B = 0.67. 75% yield. ^1H NMR ($CDCl_3$): δ 3.03 (2H, t, $J_{H,H}$7Hz, βCH_2); 3.75 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3); 4.47 (2H, q, $J_{H,P}$7Hz, αCH_2); 7.10-7.73 (3H, m, protons *para* and *meta* to pyridyl nitrogen); 8.63 (1H, d, J_{ortho}5Hz, proton *ortho* to

pyridyl nitrogen). MS: m/e 231 (M^+). (Found: C, 47.0; H, 6.20; N, 5,90%. $C_9H_{14}ONP$ requires C, 46.75; H, 6.06; N, 6.06%).

Dimethyl-(quinolin-8-yl) phosphate, C. C was prepared according to the "alkoxide" procedure described earlier. The crude product was purified by stirring overnight in pet. ether so to remove traces of grease still present from the NaH dispersion. 75% yield, m.p. pale yellow solid = 69-71°C. ^1H NMR ($CDCl_3$): δ 4.07 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3); 7.38-7.90 (4H, m, ring protons in positions 3, 5, 6 and 7); 8.23 (1H, d of d, J_{ortho}9Hz, J_{meta}1Hz ring proton *para* to N atom); 9.10 (1H, d of d, J_{ortho}5Hz, J_{meta}1Hz ring proton *ortho* to N atom). MS: m/e 253 (M^+). (Found: C, 52.5; H, 4.75; N, 5.50%. $C_{11}H_{12}NPO_4$ requires C, 52.18; H, 4.78; N, 5.53%).

Dimethyl-(4-pyridylmethyl) phosphate, D. The general "alkoxide" method was followed and yielded a brown red oil which was purified by column chromatography.

Chromatographic separation 1: the crude product was chromatographed using 20% ethanol in chloroform giving a red oil. This fraction was identified by ^1H NMR spectroscopy and was found to contain D and 4-pyridiniummethanol chloride in a 6:1 ratio.

Chromatographic separation 2: the contaminated product was purified by column chromatography eluting with 14% ethanol in chloroform. 25% yield. ^1H NMR ($CDCl_3$): δ 3.83 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3); 5.16 (2H, d, $J_{H,P}$7Hz, CH_2); 7.32 (2H, d of d, J_{ortho}5Hz, J_{meta}2Hz protons *meta* to pyridyl nitrogen); 8.65 (2H, d of d, J_{ortho}5Hz, J_{meta}2Hz protons *ortho* to pyridyl nitrogen). MS: m/e 217 (M^+).

Methyl-[2-(N-methylpyridinium)methyl] phosphate, 4.1. The zwitterion was isolated from the product mixture of A which had been heated in D_2O at 60°C for 6 days, by reverse phase column chromatography eluting with 20% water in methanol. r.f. 4.1 = 0.76. The product was further purified by recrystallization from isopropanol. 79% yield, m.p. 205-208°C, with decomposition. ^1H NMR (D_2O): δ 3.64 (3H, d, $J_{H,P}$11Hz, OCH_3); 4.42 (3H, s, $\overset{+}{N}-CH_3$); 5.43 (2H, d, $J_{H,P}$9Hz, CH_2); 7.97-9.02 (4H, m, pyridyl protons). (Found: C, 43.95; H, 5.60; N, 6.50%. $C_8H_{12}O_4PN$ requires C, 44.25; H, 5.57; N, 6.45%.

Dimethyl-[2-(N-methylpyridinium)methyl] phosphate methylsulphate, AI^+. 2.5 ml dimethyl sulphate was added dropwise to 0.553 g A (2.55×10^{-3} mol) with stirring. The mixture was heated for 1 h at 100°C in an oil bath and then left stirring overnight at room temperature. Excess dimethyl sulphate was removed by washing with 4 x 4 ml aliquots dry ether and with 2 x 4 ml aliquots dry benzene. The product oil was dried *in vacuo*. Yield 98%. ^1H NMR (D_2O): δ 3.78 (3H, s, $SOCH_3$); 3.97 (6H, d, $J_{H,P}$11Hz, 2 x $POCH_3$); 4.43 (3H, s, $\overset{+}{N}-CH_3$); 5.68 (2H, d, $J_{H,P}$9Hz, CH_2); 8.03-9.17 (4H, m, pyridyl protons). In addition, the ^1H NMR spectrum revealed the presence of dimethyl sulphate (5%), δ 4.08 (6H, s, 2 x $SOCH_3$).

Sodium Methyl-(2-pyridylmethyl) phosphate, AI^-. The synthetic procedure used in the attempt to synthesize AI^- is described in ch. 4.1.3.

(2-pyridylmethyl) acetate, E. To a solution of 0.5 g anhydrous $ZnCl_2$ in 10 ml acetic anhydride which had been heated for 10 min.,

was slowly added 0.05 mol 2-pyridylmethanol. The mixture was refluxed for 1 h, cooled, poured into iced water and stirred vigorously. After neutralization with NaOH, extraction with ethyl acetate and drying, the solvents were evaporated under reduced pressure leaving the crude product. This was purified by column chromatography eluting with 20% ethanol in chloroform. r.f. E = 0.92. Yield 56%. ^{1}H NMR ($CDCl_3$): δ 2.18 (3H, s, CH_3); 5.30 (3H, s, CH_2); 7.13-8.0 (3H, m, protons *para* and *meta* to pyridyl N); 8.71 (1H, d of d, J_{ortho}5Hz, J_{meta}2Hz proton *ortho* to pyridyl N). MS: m/e 151 (M^+). (Found: C, 63.70; H, 6.10; N, 9.20%. $C_8H_9NO_2$ requires C, 63.56; H, 6.0; N, 9.27%).

β-(2-pyridylethyl) acetate, F. A solution of 1 g anhydrous $ZnCl_2$ and 40 ml acetic anhydride (10-fold excess) was heated for 10 min. After cooling, 0.05 mol β-(2-pyridyl)-ethanol was added and the mixture left to stir at room temperature for 18 h. This was then poured into iced water and stirred vigorously. The product mixture was neutralized, extracted into ethyl acetate and dried over anhydrous $MgSO_4$. After filtering, the product mixture obtained by removal of the solvent was subsequently subject to column chromatography using 10% ethanol in chloroform as eluant. r.f. F = 0.82. Yield 65%. ^{1}H NMR ($CDCl_3$): δ 2.03 (3H, s, CH_3); 3.13 (2H, t, $J_{H,H}$7Hz, αCH_2); 4.50 (2H, t, $J_{H,H}$7Hz, βCH_2); 7.05-7.90 (3H, m, protons *para* and *meta* to pyridyl N); 8.63 (1H, d of d, J_{ortho}5Hz, J_{meta}1Hz proton *ortho* to pyridyl N). MS: m/e 165 (M^+). (Found: C, 65.05; H, 6.65; N, 8.20%. $C_9H_{11}NO_2$ requires C, 65.45; H, 6.67; N, 8.48%).

8-quinolyl acetate, G. Anhydrous sodium acetate (ground) (0.01 mol) was weighed into the reaction vessel and immediately covered

with acetic anhydride (5 ml). 8-hydroxyquinoline (0.027 mol) was added and the mixture heated for 2 h at 80°C. When cool, the product mixture was poured onto 30 g crushed ice. The precipitate which resulted was collected by filtration and washed thoroughly with ice cold water. The product was dried over P_4O_{10} and NaOH pellets. Yield 85%. m.p. 55-57°C. ^{1}H NMR ($CDCl_3$): δ 2.52 (3H, s, CH_3); 7.33-7.97 (4H, m, ring protons in positions 3, 5, 6 and 7); 8.25 (1H, d of d, J_{ortho} 5Hz, J_{meta} 1Hz, proton *para* to quinolyl N); 9.00 (1H, d of d, J_{ortho} 5Hz, J_{meta} 1Hz proton *ortho* to quinolyl N). (Found: C, 70.65; H, 4.95; N, 7.55%. $C_{11}H_9NO_2$ requires C, 70.59; H, 4.81; N, 7.49%).

Methyl-[8-(N-methylquinolinium)] phosphate, 5.1.

Experiment A: A solution of 100 mg dimethyl-(quinolin-8-yl) phosphate C and 25 µl CH_3I in 0.5 ml CD_3COCD_3 was prepared in an NMR tube. TMS was added as internal standard. To prevent evaporation of the volatile materials during the preparation of the sample, the NMR tube was immersed in a dry ice/acetone mixture. The ^{1}H NMR spectrum was recorded to ensure that the ratio of C to CH_3I was 1:1. The NMR tube was sealed and placed in a water bath at 60°C. After 12 days, the needle-shaped crystals were obtained from the NMR tube by first decanting the acetone solution and then by drying the tube in a dessicator. The crystals were purified by recrystallization from nitromethane. Yield 88%, m.p. 195°C with decomposition. ^{1}H NMR (D_2O): δ 3.85 (3H, d, $J_{H,P}$ 11Hz, OCH_3); 4.93 (3H, s, $\overset{+}{N}$-CH_3); 7.93-8.28 (4H, m, ring protons in positions 3, 5, 6 and 7); 9.04-9.37 (2H, m, protons *ortho* and *para* to quinolyl N). (Found: C, 51.0; H, 4.75; N, 5.44%. $C_{11}H_{12}O_4NP$ requires C, 52.17; H, 4.74; N, 5.53%).

Dimethyl-[8-(N-methylquinolinium)] phosphate trifluoromethanesulfonate, CI^+. 0.22 ml (2×10^{-3} mol) methyl trifluoromethanesulfonate was added to 2×10^{-3} mol dimethyl-(quinolin-8-yl) phosphate dissolved in 5 ml nitromethane. The reaction was exothermic. The solution was allowed to cool to room temperature and then ether was added dropwise until the first sign of cloudiness appeared. The reaction flask was stoppered and left in a refrigerator overnight. The solvents were removed under reduced pressure giving a thick, viscous orange-coloured oil. 84% yield. ^{1}H NMR (D_2O): δ 4.33 (6H, d, $J_{H,P}$11Hz, 2 x OCH_3); 4.98 (3H, s, $\overset{+}{N}$-CH_3); 7.96-8.47 (4H, m, ring protons at positions 3, 5, 6 and 7); 9.13-9.46 (2H, m, protons *para* and *ortho* to quinolyl N). (Found: C, 36.65; H, 4.20; N, 3.90%. $C_{13}H_{15}NO_7PF_3S$ requires C, 37.41; H, 3.60; N, 3.36%).

Mono-sodium salt of 8-quinolylmethyl phosphate, CI^-. 4×10^{-3} mol dimethyl-(quinolin-8-yl) phosphate and 4×10^{-3} mol NaI were dissolved in 30 ml acetone and refluxed for 4 h using an air condenser. After cooling, the pale yellow solid was collected by centrifugation and washed with ether. The crude product was purified by dissolving it in 5 ml acetonitrile and then pouring directly into 20 ml dry ether. The fine white precipitate which immediately formed was collected by centrifugation and dried in a dessicator over P_4O_{10}. 90% yield, m.p. undetermined due to hygroscopic nature of salt. ^{1}H NMR (D_2O): δ 3.75 (3H, d, $J_{H,P}$11Hz, OCH_3); 7.36-7.74 (4H, m, ring protons at positions 3, 5, 6 and 7); 8.22 (1H, d of d, J_{ortho}9Hz, J_{meta}1Hz proton *para* to quinolyl N); 8.76 (1H, d of d, J_{ortho}5Hz, J_{meta}1Hz proton *ortho* to quinolyl N). (Found: C, 43.02; H, 3.98; N, 5.02%. $C_{10}H_9NO_4PNa.H_2O$ requires C, 43.01; H, 3.94; N, 5.02%).

8-hydroxy-(N-methylquinolinium) iodide. 0.5 g 8-hydroxyquinoline and 21 ml MeI were left to stand at room temperature in a stoppered flask. After 6 days, the brown crystals were collected by filtration and recrystallized from propanol/water. m.p. 136-138°C. ^{1}H NMR (D_2O): δ 4.82 (3H, s, $\overset{+}{N}$-CH_3); 7.33-7.96 (4H, m, ring protons in positions 3, 5, 6 and 7); 8.78-9.00 (2H, m, protons *ortho* and *para* to quinolyl N). (Found: C, 39.55; H, 3.90; N, 4.55%. $C_{10}H_{10}NIO.H_2O$ requires C, 39.34; H, 3.93; N, 4.59%).

N-methylpyridinium iodide was prepared by addition of an equimolar amount of MeI (1.8 g) to a solution of pyridine (1.02 g) in benzene at room temperature. After 1 h, the product was collected by filtration, washed with benzene and dried. Yield 85%. ^{1}H NMR (D_2O): δ 4.42 (3H, s, $\overset{+}{N}$-CH_3); 8.02-9.13 (5H, m, C_5H_5N). (Found: C, 32.64; H, 3.51; N, 6.46%. C_6H_8NI requires C, 32.58; H, 3.62; N, 6.33%).

4-dimethylamino-1-methylpyridinium iodide was prepared by addition of a 10-fold excess of MeI (8×10^{-3} mol) to a solution of 4DMAP (0.1 g) in ethanol at room temperature. After 1 h, the crystalline product was collected, washed with ethanol and recrystallized from propan-2-ol. 92% yield, m.p. 246-247°C (lit. 248-249°C). ^{1}H NMR (D_2O): δ 3.20 (6H, s, $(CH_3)_2N$); 3.90 (3H, s, $\overset{+}{N}$-CH_3); 6.78-8.13 (4H, m, C_6H_4). (Found: C, 36.50; H, 4.80; N, 10.70%. $C_8H_{13}N_2I$ requires C, 36.36; H, 4.92; H, 10.61%).

Ethyl (β-phenylethyl)phosphorochloridate, 9.1a. A mixture of 9.82 g (0.0805 mol) β-phenylethanol and 11.1 ml (0.0805 mol) triethylamine in 40 ml freshly distilled ether was added dropwise to an ice/salt bath cooled and magnetically stirred etheral solution of $EtOP(O)Cl_2$ (26.24 g, 0.16 mol). The temperature was maintained at below 10°C during the addition (0.5 h). Stirring was continued for 1.5 h at room temperature. The white precipitate of triethylammonium chloride was removed by filtration and the ether removed from the filtrate under reduced pressure leaving a clear liquid. The ^1H NMR spectrum of the liquid showed that it consisted of 50 mole % $EtOP(O)Cl_2$ and 50 mole % desired product. The excess $EtOP(O)Cl_2$ was distilled as a colourless liquid, b.p. 34-40°C/0.5-1.0mm. The ^1H NMR spectrum ($CDCl_3$) of the undistilled product indicated less than 5% $EtOP(O)Cl_2$ remained. The product was divided into 2 portions. The one portion was distilled, b.p. 130-137°C/0.4 mm as an orange/brown liquid. ^1H NMR spectroscopy revealed that this was a mixture of 85 mole % desired product and 15 mole % β-phenylchloroethane - the latter identified by comparison with authentic sample. ^1H NMR ($CDCl_3$) undistilled portion: δ1.32 (3H, d of t, $J_{H,H}$7Hz, $J_{H,P}$2Hz, βCH_3); 3.03 (2H, t, $J_{H,H}$7Hz, βCH_2); 3.95-4.60 (6H, m, 2 x $\underline{CH_2}CH_2$ and CH_2OP); 7.35 (5H, s, C_6H_5). MS: m/e 248 (M^+, r.a. <5%). (Found: C, 48.70; H, 5.80%. $C_{10}H_{14}O_3PCl$ requires C, 48.29; H, 5.63%).

(β-phenylethyl)phosphorodichloridate, 9.1b. To 4.9 g (0.032 mol) freshly distilled $POCl_3$ in 40 ml ether, was added dropwise to an ethereal solution containing 2.56 g (0.021 mol) of β-phenylethanol. The reaction mixture was stirred and cooled in an ice/salt bath to keep the temperature between 0-5°C during the addition. The

reaction mixture was maintained at this temperature with stirring for a further 1.5 h. The ether was removed under reduced pressure on a rotary evaporator leaving a pale yellow oil. The crude product was distilled, b.p. 100-103°C/0.4 mm, colourless oil. Yield 75%. ^{1}H NMR ($CDCl_3$): δ 3.09 (2H, t, $J_{H,H}$7Hz, βCH$_2$); 4.48 (2H, d of t, $J_{H,P}$10.5Hz, $J_{H,H}$7Hz, αCH$_2$); 7.27 (5H, s, C_6H_5). MS: no m/e 238 (M^+). (Found: C, 40.60; H, 3.90%. $C_8H_9O_2PCl_2$ requires C, 40.34; H, 3.80%).

Bis-(β-phenylethyl)phosphorochloridate, 9.1c. 3.4 ml (0.039 mol) PCl_3 and 25 ml benzene were measured into a 250 ml 3-necked round bottom flask equipped with low temperature thermometer, drying tube and dropping funnel. 9.27 g (0.76 mol) β-phenylethanol and 10.09 g (0.082 mol) N,N-dimethylaniline were dissolved in 25 ml benzene and placed in the dropping funnel. This mixture was added dropwise to the reaction flask with stirring and cooling in ice over a period of 1 h, maintaining the temperature at 5-12°C. Stirring was then continued for 1 h at room temperature. 10 ml water was added and the mixture stirred for a further 2 h. Evolution of HCl necessitated replacement of the drying tubes periodically. The aqueous layer was washed with 3 x 10 ml aliquots benzene and the combined benzene layers washed with 10 ml Na_2CO_3 (5%), 10 ml water and then dried over anhydrous $MgSO_4$. The benzene was removed *in vacuo* to give a colourless mobile oil, which was found by ^{1}H NMR spectroscopy to contain the desired bis-(β-phenylethyl) phosphite (56 mole %) and unreacted alcohol (44 mole %). β-phenylethanol was removed by distillation (b.p. 54°C/0.2mm), and the product distilled as a fluorescent oil, b.p. 173-175°C/0.2mm. Yield 50%. ^{1}H NMR ($CDCl_3$): δ 2.89 (4H, t, $J_{H,H}$7Hz, 2 x βCH$_2$);

4.13 (4H, m, $J_{H,P}=J_{H,H}$7Hz, 2 x αCH_2); 6.57 (1H, d, $J_{H,P}$698Hz, PH); 7.21 (10H, s, 2 x C_6H_5). (Found: C, 66.05; H, 6.70%. $C_{16}H_{19}O_3P$ requires C, 66.21; H, 6.55%).

To 2.9 g (0.01 mol) purified bis-(β-phenylethyl) phosphite suspended in 30 ml CCl_4 was added dropwise with stirring and cooling the reaction vessel in an ice-bath, 1.39 g (0.01 mol) SO_2Cl_2 in 5 ml CCl_4. The reaction mixture was kept under an atmosphere of N_2, and left to stir for 2 h, the drying tubes being replaced periodically. The evolved gases, excess SO_2Cl_2 and solvent were removed under reduced pressure at room temperature giving a colourless oil. Yield 97%. ^{1}H NMR ($CDCl_3$): δ 2.92 (4H, t, $J_{H,H}$7Hz, 2 x βCH_2); 4.29 (4H, q, $J_{H,P}=J_{H,H}$7Hz, 2 x αCH_2); 7.25 (10H, s, 2 x C_6H_5). MS: no m/e 324 (M^+). (Found: C, 59.15; H, 5.55%. $C_{16}H_{18}O_3PCl$ requires C, 59.18; H, 5.55%).

Ethyl (β-phenylethyl) p-nitrophenyl phosphate, 9.1d was prepared by direct addition of 0.65 g (4.03×10^{-3} mol) NaOPNP to a cooled solution (T = 10°C) of 1 g (4.03×10^{-3} mol) 9.1a dissolved in 50 ml ether. The reaction mixture was stirred at this temperature for 2 h and then overnight ar room temperature. The product was obtained after filtering the NaCl and removing the ether under vacuum. ^{1}H NMR spectroscopy showed that it was contaminated with PNPOH (17 mole %). Column chromatography (alumina) using $CHCl_3$:pet. ether (1:1) as eluant was used to purify the product. Yield 29%. ^{1}H NMR ($CDCl_3$): δ 1.32 (3H, t, $J_{H,H}$7Hz, βCH_3); 3.00 (2H, t, $J_{H,H}$7Hz, βCH_2); 3.98-4.54 (4H, m, αCH_2); 7.10-7.46 (7H, m, C_6H_5 and 2H *meta* to NO_2); 8.40 (2H, d, J_{ortho}9Hz, 2H *ortho* to NO_2). MS: m/e 351 (M^+, r.a. <3%). (Found: C, 54.60; H, 5.50; N, 3.80%. $C_{16}H_{18}O_6NP$ requires C, 54.70; H, 5.13; N, 3.99%).

Bis-(β-phenylethyl) p-nitrophenyl phosphate, 9.1e was prepared by adding 0.32 g (2.02×10^{-3} mol) NaOPNP directly to a cooled solution (T = 10°C) of 0.65 g (2.02×10^{-3} mol) 9.1c dissolved in 50 ml ether. The reaction mixture was stirred for 2 h at 10°C and then overnight at room temperature. After 28 h, the orange colour due to NaOPNP had disappeared. The white precipitate (NaCl) was filtered using gravity filtration, washed with ether and the ether removed *in vacuo* to give a pale pink oil. The ^{1}H NMR spectrum of the crude product showed contamination by PNPOH (10 mole %). PNPOH was removed by dissolving the product in 8 ml ether and washing rapidly with 5 ml NaOH (5%) and 5 ml water. The etheral solution was dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* giving a pale yellow oil. Yield 85%. ^{1}H NMR ($CDCl_3$): δ 2.93 (4H, t, $J_{H,H}$7Hz, 2 x βCH_2); 4.28 (4H, q, $J_{H,P}=J_{H,H}$7Hz, 2 x αCH_2); 6.97-7.33 (12H, m, 2 x C_6H_5 and 2H *meta* to NO_2); 8.17 (2H, d, J_{ortho}9Hz, 2H *ortho* to NO_2). MS: m/e 427 (M^+, r.a. <2%); (Found: C, 61.90; H, 5.35%. $C_{22}H_{22}O_6PN$ requires C, 61.83; H, 5.15%).

[β-(p-methoxyphenyl)ethyl]phosphorodichloridate, 9.1f. 3.3 g (0.0215 mol) $POCl_3$ was dissolved in 30 ml ether and placed in a 100 ml 3-necked flask equipped with a low temperature thermometer, dropping funnel and a drying tube. 2.04 g (0.013 mol) β-(p-methoxyphenyl)ethyl alcohol was dissolved in 40 ml ether and added dropwise with stirring to the reaction vessel with external cooling (T = -20 - -15°C). The addition took 0.5 h and the reaction mixture was stirred for a further 1.5 h at this temperature. Excess $POCl_3$ and the solvent were removed under reduced pressure at room temperature to give a burgundy coloured oil. Yield 98%. ^{1}H NMR

($CDCl_3$): δ 2.02 (2H, t, $J_{H,H}$7Hz, αCH_2); 2.77 (3H, s, CH_3O); 3.18-3.67 (2H, d of t, $J_{H,H}$7Hz, $J_{H,P}$10.5Hz, αCH_2); 6.70-7.30 (4H, m, C_6H_4). (Found: C, 43.80; H, 5.30%. $C_9H_{11}O_3PCl_2$ requires C, 40.15; H, 4.09%).

Bis-[β-(p-methoxyphenyl)ethyl]phosphorochloridate, 9.1g. A mixture of 4.28 g (0.028 mol) β-(p-methoxyphenyl)ethyl alcohol and 3.7 g (0.030 mol) N,N-dimethylaniline dissolved in 20 ml benzene was added to a stirred solution of 1.97 g (0.014 mol) PCl_3 in 20 ml benzene. The temperature was maintained at 8-10°C by cooling in an ice/salt bath and moisture was excluded. The reaction mixture was then stirred for 16 h at room temperature. 5 ml water was added and the reaction mixture stirred vigorously for 0.5 h. The benzene layer was extracted, neutralized with 10 ml Na_2CO_3 (5%) and washed several times with water. After drying with anhydrous $MgSO_4$, the benzene was removed under reduced pressure to give the crude product, found by ^1H NMR spectroscopy to consist of the target compound and traces of N,N-dimethylanilinium chloride. This salt was removed by redissolving the crude mixture in 10 ml benzene and washing with 10 ml HCl (5%) and 3 x 10 ml water. The solution was concentrated under reduced pressure to give the phosphite as a colourless oil. Yield 75%. ^1H NMR ($CDCl_3$): δ 2.87 (4H, t, $J_{H,H}$7Hz, 2 x βCH_2); 3.73 (6H, s, 2 x OCH_3); 4.14 (4H, q, $J_{H,P}=J_{H,H}$7Hz, 2 x αCH_2); 6.60 (1H, d, $J_{H,P}$702Hz, PH); 6.70-7.30 (8H, m, 2 x C_6H_4). (Found: C, 61.95; H, 6.55%. $C_{18}H_{23}O_5P$ requires C, 61.70; H, 6.57%).

Bis-[β-(p-methoxyphenyl)ethyl]phosphorochloridate was then prepared by passing a slow stream of N_2 through a stirred solution of 2.48 g (7.09×10^{-3} mol) bis-[β-(p-methoxyphenyl)ethyl] phosphite in 30 ml

CCl_4 while 1 g (7.4×10^{-3} mol) SO_2Cl_2 in 10 ml CCl_4 was added over 0.5 h (T = -10 - -5°C). N_2 was then blown through the orange coloured solution at a more rapid rate for 4 h at room temperature and with stirring. The evolved gases, excess starting material and solvent were removed at room temperature under reduced pressure (20 mm) and the reaction flask then left for 3 h at 0.4 mm. Yield 96%. ^{1}H NMR ($CDCl_3$): δ 2.93 (4H, t, $J_{H,H}$7Hz, 2 x βCH_2); 3.77 (6H, s, 2 x OCH_3); 4.28 (4H, q, $J_{H,H}$7Hz, 2 x αCH_2); 6.73-7.32 (8H, m, 2 x C_6H_4). (Found: C, 54.55; H, 5.60%. $C_{18}H_{22}O_5PCl$ requires C, 56.18; H, 5.72%).

Bis-[β-(p-methoxyphenyl)ethyl] p-nitrophenyl phosphate, 9.1h was prepared by adding 1.71 g (0.0118 mol) NaOPNP directly to 4.55 g (0.0118 mol) 9.1g dissolved in 40 ml ether. The reaction mixture was stirred for 42 h at room temperature. Precipitated NaCl was removed by gravity filtration and the product washed with 5 ml NaOH (5%) and 2 x 10 ml water. The etheral solution was dried over anhydrous $MgSO_4$ and the Et_2O removed *in vacuo* to give a viscous orange/brown oil. Yield 81%. ^{1}H NMR ($CDCl_3$): δ 2.88 (4H, t, $J_{H,H}$7Hz, 2 x βCH_2); 3.77 (6H, s, 2 x OCH_3); 4.28 (4H, q, $J_{H,H}$= $J_{H,P}$7Hz, 2 x αCH_2); 6.73-7.33 (10H, m, 2 x C_6H_4 + 2H *meta* to NO_2); 8.15 (2H, d, J_{ortho} 8Hz, 2H *ortho* to NO_2). MS: no m/e 487 (M^+). (Found: C, 58.75; H, 5.30; N, 2.60%. $C_{24}H_{26}O_8NP$ requires C, 59.14; H, 5.34; N, 2.87%).

Diethyl (β-phenylethyl) phosphate, 9.1i. I. A solution of 9.83 g (0.0806 mol) β-phenylethanol and 8.14 g (0.0806 mol) Et_3N in 40 ml ether was added dropwise to 27.8 g (0.16 mol) $(EtO)_2P(O)Cl$ in 40 ml ether with stirring and cooling the reaction mixture in ice so keeping the temperature below 10°C. After addition, the mixture

was stirred for 1.5 h at room temperature. The precipitated triethylammonium chloride was removed by suction and then gravity filtration. The ether was removed *in vacuo* to yield a colourless oil contaminated with the triethylammonium chloride. After first testing on a small scale, the following procedure was followed. 20 ml Water and 20 ml benzene were added to the filtrate and the benzene extracted, dried over anhydrous $MgSO_4$, and then the benzene removed *in vacuo* to leave a colourless oil. This was shown by ^1H NMR spectroscopy to be a mixture of the desired product (0.5 mole fraction) and unreacted β-phenylethanol (0.5 mole fraction). Chromatographic separation on a small scale was attempted using $CHCl_3$:EtOH (24:1) as eluant (r.f. $PhCH_2CH_2OH$ = 0.64; r.f. product = 0.77). This gave a clear oil. ^1H NMR ($CDCl_3$): δ 1.30 (3H, t, $J_{H,H}$7Hz, 2 x CH_3); 3.03 (2H, t, $J_{H,H}$7Hz, βCH_2); 3.83-4.48 (6H, m, 3 x αCH_2); 7.40 (5H, s, C_6H_5). (Found: C, 55.60; H, 7.40%. $C_{12}H_{19}O_4P$ requires C, 55.81; H, 7.42%). Attempts to purify the remainder of the crude product under the same conditions were unsuccessful and the product was found by ^1H NMR and mass spectroscopy to contaminated with $(EtO)_3PO$ formed by ethanolysis of 9.1i.

II. A mixture of 3.72 g (0.030 mol) β-phenylethanol and 2.4 g (0.030 mol) pyridine were placed in a 50 ml round botom flask. 5.24 g (0.030 mol) $(EtO)_2P(O)Cl$ was added dropwise with stirring and cooling (T = 10°C). The mixture was stirred for 3 h at room temperature with protection from moisture. The precipitated pyridinium chloride was removed by gravity filtration and then by washing the ether solution with 10 ml water. The ether layer was dried over anhydrous $MgSO_4$ and the ether removed *in vacuo* to give

a mobile liquid. The crude product was shown by ^{1}H NMR spectroscopy to consist of 88 mole % 9.1i and 12 mole % unreacted alcohol. The crude product was purified by distillation, b.p. 144°C/5 mm. Yield 68%. The ^{1}H NMR spectrum showed the same spectral characteristics as the previous spectrum. MS: m/e 258 (M^+, r.a. <2%); m/e 104 (r.a. 100%). (Found: C, 54.60; H, 7.60%. $C_{12}H_{19}O_4P$ requires C, 55.81; H, 7.42%).

β-phenylchloroethane[176] was prepared by adding dropwise with cooling, 3.48 g (0.095 mol) conc. HCl to 13 g (0.095 mol) anhydrous $ZnCl_2$. 5.82 g (0.048 mol) β-phenylethanol was added and the mixture refluxed for 3 h. 30 ml H_2O and 30 ml benzene was added, the benzene layer separated and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give a colourless oil which was found by ^{1}H NMR spectroscopy to be a mixture of the product (75 mole %) and starting alcohol (25 mole %). The crude product was purified by column chromatography using chloroform as eluant (r.f. product = 0.92; r.f. alcohol = 0.41). Yield 65%. ^{1}H NMR ($CDCl_3$): δ 3.02 (2H, t, $J_{H,H}$7Hz, CH_2Cl); 3.67 (2H, t, $J_{H,H}$7Hz, $\underline{CH_2}CH_2Cl$); 7.23 (5H, s, C_6H_5). MS: m/e 140 (M^+, r.a. 91%). (Found: C, 68.60; H, 6.70%. C_8H_9Cl requires C, 68.30; H, 6.47%).

β-(p-methoxyphenyl)ethyl alcohol was prepared from a solution of 2.42 g (0.064 mol) $LiAlH_4$ in 90 ml ether which was placed in a 500 ml 3-necked flask equipped with a reflux condensor, dropping funnel and mechanical stirrer and protected from moisture. A solution of 8.66 g (0.052 mol) β-(p-methoxyphenyl) acetic acid in 75 ml ether was added at a rate such as to produce gentle reflux. The reaction mixture was stirred for 1.5 h at room temperature. 5 ml water was added dropwise with cooling to decompose

excess hydride. After 0.5 h, a further 5 ml water was added. The procedure was repeated once more after which the flask was left to stir overnight at room temperature. A copious off-white precipitate of $LiAl(OH)_4$ was observed. 8 ml H_2SO_4 (10%) was added with cooling of the flask and resulted in a clear solution. The product was extracted with 5 x 15 ml aliquots ether, dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* to give a cream solid. Yield 84%, m.p. 21-23°C. ^{1}H NMR ($CDCl_3$): δ 2.24 (1H, s, OH, signal disappears with D_2O wash); 2.74 (2H, t, $J_{H,H}$7Hz, $\underline{CH_2}CH_2OH$); 3.70 (3H, s, OCH_3); 3.70 (2H, t, $J_{H,H}$7Hz, CH_2OH); 6.67-7.18 (4H, m, C_6H_4). (Found: C, 71.00; H, 7.30%. $C_9H_{12}O_2$ requires C, 71.05; H, 7.89%).

<u>β-(p-methoxyphenyl)chloroethane</u> was prepared by adding dropwise with cooling, 1.22 g (0.033 mol) conc. HCl to 4.55 g (0.033 mol) anhydrous $ZnCl_2$. 2.54 g (0.017 mol) β-(p-methoxyphenyl)ethanol was crushed finely and added directly to the mixture which darkened in colour. The mixture was refluxed for 5 h and then stirred overnight at room temperature. 10 ml H_2O and 10 ml benzene were added, the benzene layer separated and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* and the crude reaction mixture was found by ^{1}H NMR spectroscopy to consist of 80% desired product and 20% starting alcohol. The first column chromatographic separation using $CHCl_3$:$(CH_3)_2CO$ (9:1) did not give a chromatographically homogeneous product. A second column was prepared with pet. ether:CH_2Cl_2 (3:1) as eluant and this yielded pure product. Yield 67%. ^{1}H NMR ($CDCl_3$): δ 2.96 (2H, t, $J_{H,H}$7Hz, CH_2Cl); 3.62 (2H, t, $J_{H,H}$7Hz, $\underline{CH_2}CH_2Cl$); 3.76 (3H, s, OCH_3); 6.77-7.30 (4H, m, C_6H_4). MS: m/e 170 (M^+, r.a. 21%). (Found: C, 63.90; H, 6.80%. $C_9H_{11}OCl$ requires C, 63.36; H, 6.45%).

4-Nitrophenylphenyl ether.[177] 1 ml (0.0094 mol) 1-fluoro-4-nitrobenzene (4NFB) dissolved in 8 ml ether was added to a cooled solution of 0.57 g (0.01 mol) KOH in 11.3 ml (0.094 mol) β-phenylethanol with stirring. The reaction mixture was stirred at room temperature for 48 h. The ether was removed *in vacuo* to give a pale yellow solid product which was purified by column chromatography using $CHCl_3$ as eluant. Yield 58%, m.p. 51-53.5°C (lit.[177] 56-57°C). ^1H NMR ($CDCl_3$): δ 3.10 (2H, t, $J_{H,H}$7Hz, $\underline{CH_2}OPh$); 4.25 (2H, t, $J_{H,H}$7Hz, $\underline{CH_2}CH_2OPh$); 6.90 (2H, d, J_{ortho}9Hz, protons *meta* to NO_2); 7.27 (5H, s, C_6H_5); 8.13 (2H, d, J_{ortho}9Hz, protons *ortho* to NO_2). (Found: C, 68.90; H, 5.50; N, 5.75%. $C_{14}H_{13}NO_3$ requires C, 69.14; H, 5.35; N, 5.76%).

11.4 BASE-CATALYZED HYDROLYSIS[178]

The standard solutions of NaOH (500 ml) were prepared using a 0.1 M volumetric solution ampoule. The molarity of the stock solution was determined by titration with standard HCl solution using phenolphthalein as an indicator. The standard acid solution was prepared by diluting a volumetric ampoule of HCl to 500 ml with glass distilled water. The NaOH solution was thus found to be 0.1 M and it was used to prepare the following solutions (100 ml) of molar concentration: 2.5; 3.7; 5.0; 7.5; 10.0 x 10^{-3} M.

A stock solution of phosphate ester 2.1c (*ca.* 2.25 x 10^{-3} M) was prepared by dissolving *ca.* 49 mg of the compound in absolute ethanol and making the volume up to 50 ml. Similarly a stock solution of 2.1d (*ca.* 4.4 x 10^{-3} M) was prepared by dissolving *ca.* 48.8 mg of the compound in absolute ethanol and making the volume

up to 50 ml. Both solutions were found to be stable for at least 24 h.

For a typical kinetic run, 2.5 ml of the hydrolysis solution was placed in a 1 cm quartz cuvette and transferred to the thermostatted cell compartment of a Beckman UV-vis 5260 spectrophotometer. The phosphate ester stock solutions were brought to the reaction temperature (25°C) prior to mixing. The general procedure for the alkaline hydrolysis involved adding 40 µl of the stock solution of 2.1c or 20 µl of the stock solution of 2.1d by means of a calibrated syringe, to 2.5 ml NaOH equilibrated to the correct temperature. This gave a solution *ca.* 3.5×10^{-5} M in phosphate ester in the cuvette. The alkaline hydrolysis was followed continuously at 400 nm. The absorbance readings at this fixed wavelength were automatically recorded as a function of time against a reference of absolute ethanol (25 µl) in 2.5 ml of 3.7×10^{-3} M NaOH. The temperature variation was less than 0.2°C during a given kinetic run. All kinetic parameters were obtained using the results for one half-time of the reaction. Infinity readings were taken after 5 half-lives. Pseudo first-order rate constants (k_{obs}) were calculated from the slopes of the linear plots of $\ell n(A_\infty - A_t)$ versus time. The kinetic runs were performed in duplicate or triplicate.

11.5 O → N METHYL TRANSFER STUDIES

11.5.1

Semi-quantitative results for the rate of O → N methyl transfer in A, B, C, D, E and F were obtained by monitoring the reactions by ^{1}H NMR spectroscopy.

11.5.2

A ^{1}H NMR study on the effect of concentration on the rate of O→N methyl transfer in A, and the investigation of this reaction mechanism by ^{13}C and ^{31}P NMR spectroscopy, has been described in ch. 4.4. The ^{13}C NMR and ^{31}P NMR spectra were obtained at 22.03 MHz and 36.44 MHz respectively in 10 mm tubes using a Bruker HS-90 FT spectrometer. The ^{13}C NMR shifts are quoted relative to external dioxane in D_2O at δ = 67.4 ppm relative to TMS.[71] The ^{31}P NMR shifts are quoted relative to neat TMP present in a 2 mm coaxial capillary.

11.5.3 RATE MEASUREMENTS

The reaction of pyridine with trimethyl phosphate. A stock solution containing 1 ml TMP and 0.69 ml pyridine (1:1 mole ratio) was prepared. For a typical run, 25 µl of stock solution was transferred into a second sample tube and 500 µl of solvent added giving a concentration of 0.24 M. The solution was then transferred to an NMR tube which was sealed. The tube was thermostatted at the required temperature and the rate of reaction was monitored at each temperature by periodically withdrawing the tube from the bath, placing it in an ice-water bath (to arrest the progress of the reaction), recording the ^{1}H NMR spectrum of the sample, and returning the tube to the thermostatted bath.

For the kinetic runs with no solvent, a stock solution of 5 ml TMP (4.29×10^{-2} mol) and 3.45 ml pyridine (4.29×10^{-2} mol) was prepared. After ensuring that the mixture was homogeneous, the samples were taken directly from the stock solution.

The conversion x (expressed as a percentage of the substrate's initial concentration) was determined from the intergrated areas of the selected product signals (see ch. 8.1) relative to the total intergrated areas of substrates and products, corrected for the number of protons involved.

The reaction of 4-dimethylamino pyridine (4DMAP) with trimethyl phosphate. For the reaction in pure solvents, stock solutions of 0.035 g 4DMAP (2.88×10^{-4} mol) and 33.6 µl TMP (2.88×10^{-4} mol) in 1.2 ml of solvent were prepared. This provided enough solution, of 0.24 M concentration, for 3 samples. For the reaction in binary solvent mixtures, each sample was individually prepared from 0.0147 g 4DMAP (1.2×10^{-4} mol) and 14 µl TMP (1.2×10^{-4} mol) giving the final concentration in 0.5 ml of the binary solvent as 0.24 M. The rate of reaction was monitored and rate constants determined as described for the pyridine and trimethyl phosphate system.

11.6 CRYSTAL STRUCTURE DETERMINATION

Experimental details are described in ch. 6. The observed and calculated structure factors (F_o, F_c) are given in Appendix II.

11.7 ANCHIMERIC ASSISTANCE STUDIES

The substrates were placed in glass tubes which were sealed and placed in a thermostatted water bath at 80°C, the instant of immersion being taken as zero time. After suitable intervals, the tubes were removed and cooled in dry ice/acetone before opening. The ^1H NMR ($CDCl_3$) spectrum of the reaction mixture was then

recorded and products (as well as unchanged substrates) were identified by adding samples of authentic compounds. When chloroethane was present in a reaction product mixture, it was distilled off, trapped in a dry ice/acetone-cooled trap and identified as a single product by ^{1}H NMR spectroscopy. For 9.1b and 9.1f, the proportion of substitution to elimination product was determined directly from the ^{1}H NMR spectra of the reaction mixture. In addition, the two products were separated and identified in the following way. The mixture was refluxed with aqueous NaOH for 5 h (to remove inorganic phosphate) and the organic material separated by column chromatography ($CHCl_3$:pet. ether, 2:1). The first fraction consisted of β-arylchloroethane (identified in the usual way), and the second fraction - an amorphous solid, was identified as a polymer, formed from the corresponding styrene. In the case of polystyrene, the IR spectrum (film) and ^{1}H NMR ($CDCl_3$) spectrum were identical to the spectra of the genuine sample. For poly-(p-methoxystyrene), in addition to spectroscopic evidence, the product's composition was confirmed by elemental analysis. Found: C, 79.30; H, 8.00%. $(C_9H_{10}O)_n$ requires C, 80.60; H, 7.46%.

For substrates 9.1e and 9.1h the reaction mixture was analysed (^{1}H NMR spectroscopy and TLC) for the presence of the corresponding p-nitrophenyl-β-arylethyl ether. In both cases, as shown by the addition of a sample of authentic ether, no evidence for the formation of the ether was obtained.

Acetolysis of bis-[β-(p-methoxyphenyl)ethyl] p-nitrophenyl phosphate, 9.1h was achieved by dissolving 0.28 g (5.71×10^{-4} mol) 9.1h in 10 ml freshly distilled acetic acid and heating the

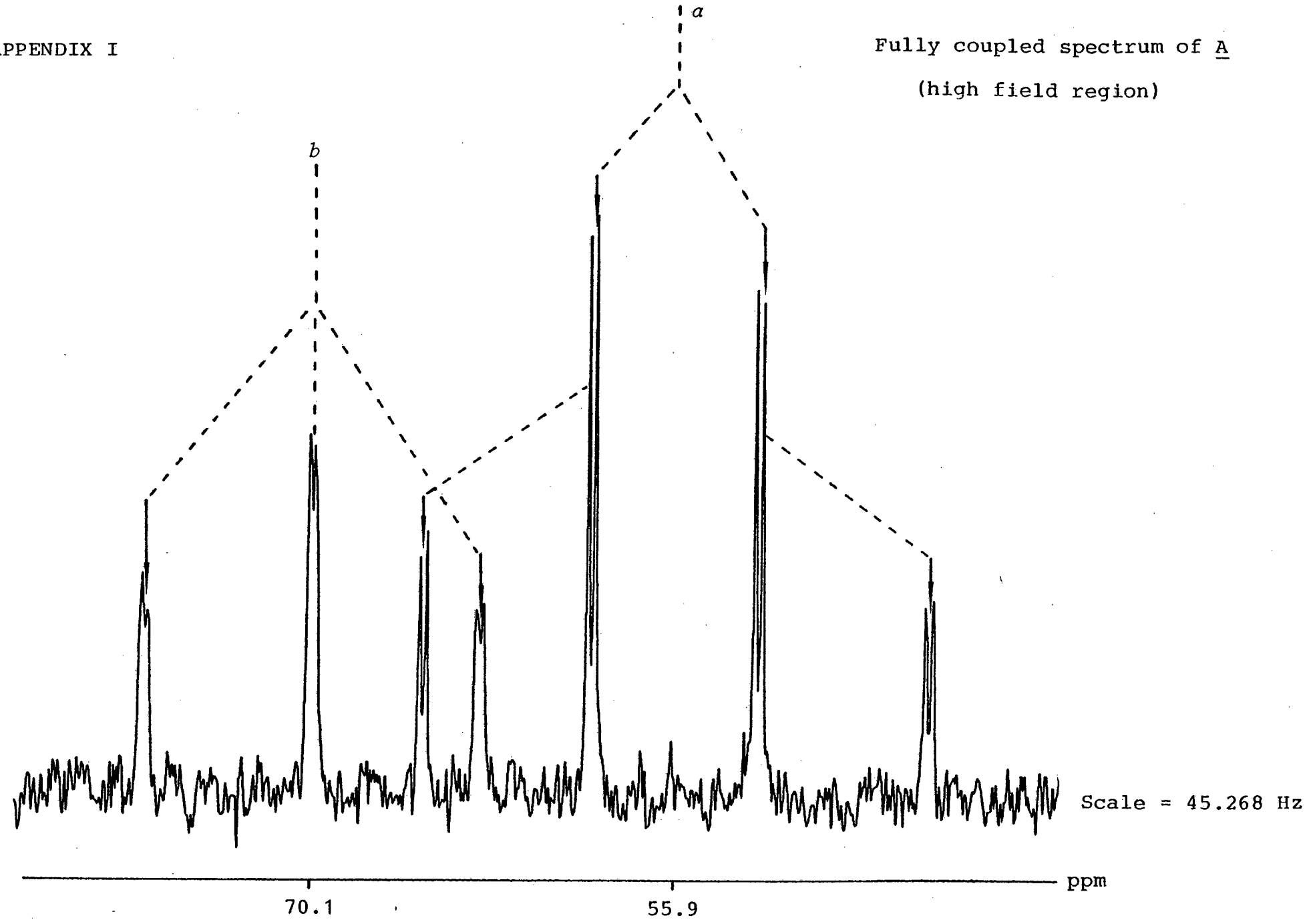
reaction mixture at 80°C in a water bath. The reaction progress was monitored by TLC ($CHCl_3$ as solvent) and by ^1H NMR spectroscopy. After 150 h, ^1H NMR spectroscopy showed the reaction had proceeded to 45%. The reaction was stopped, the acetic acid removed *in vacuo* and the product purified by column chromatography using $CHCl_3$ as eluant. ^1H NMR ($CDCl_3$): δ 2.00 (3H, s, $C(O)CH_3$); 2.85 (2H, t, $J_{H,H}$7Hz, βCH_2); 3.77 (3H, s, OCH_3); 4.21 (2H, t, $J_{H,H}$7Hz, αCH_2); 6.76-7.26 (4H, m, C_6H_4).

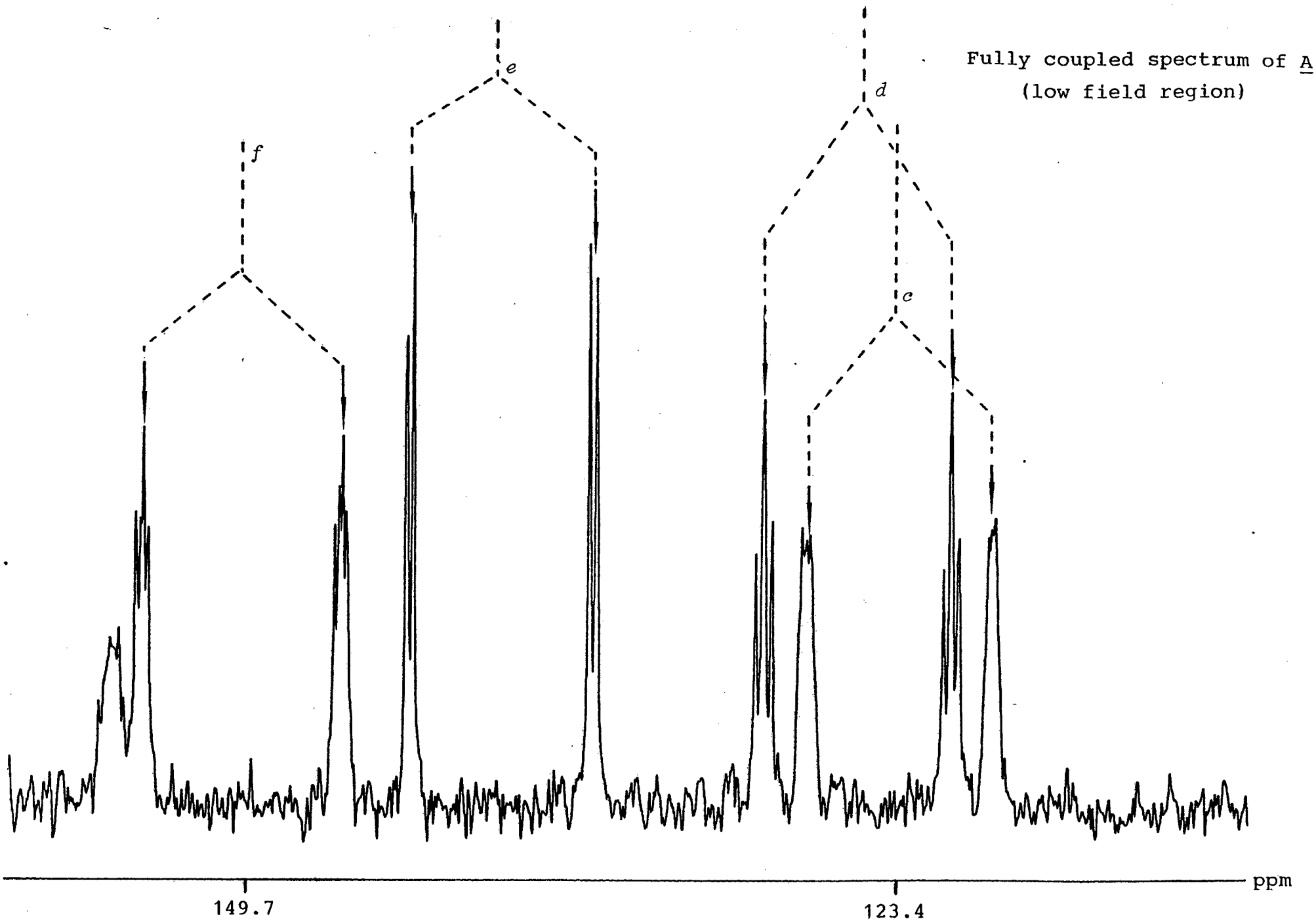
Appendix

APPENDIX I

Fully coupled spectrum of A

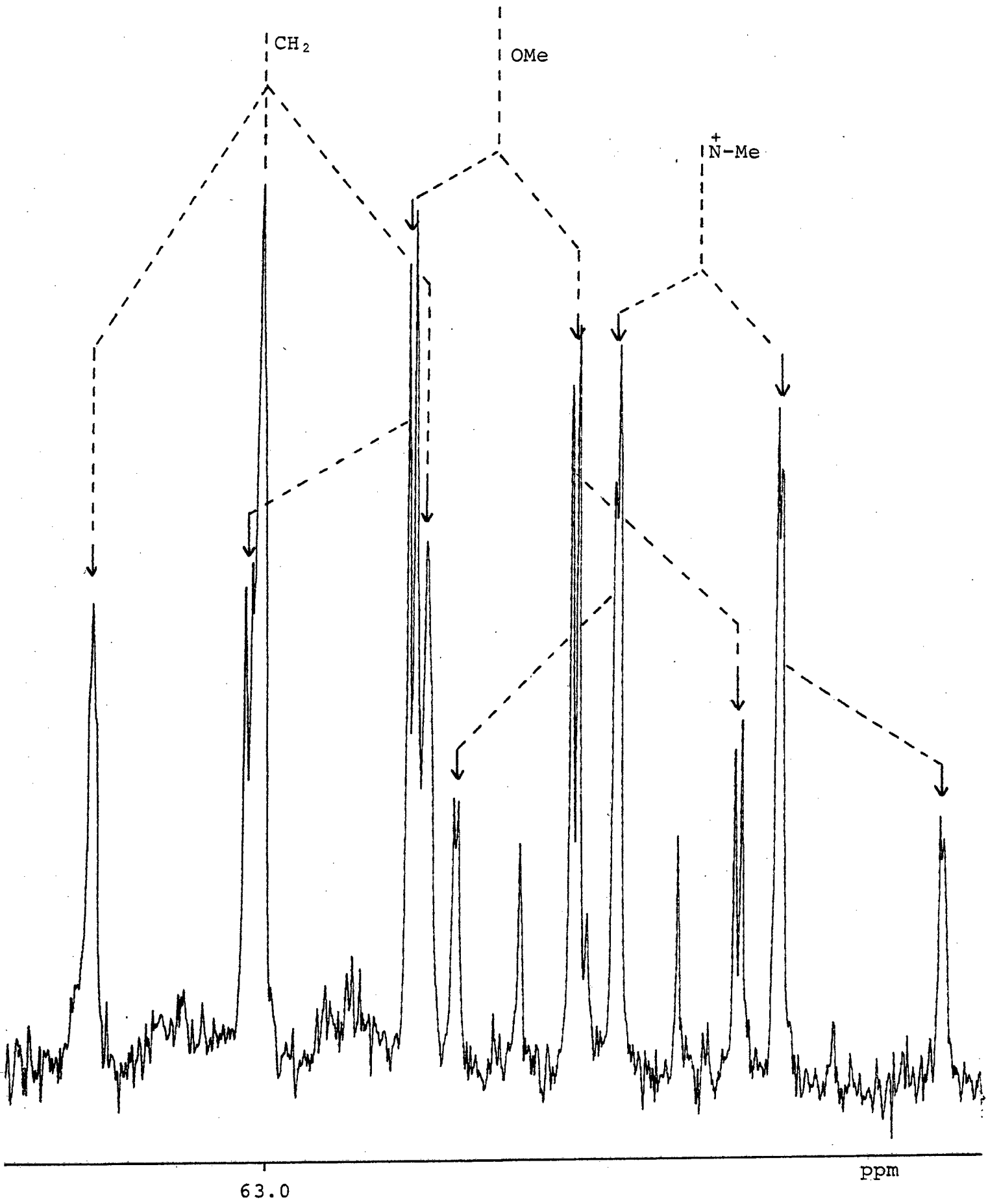
(high field region)



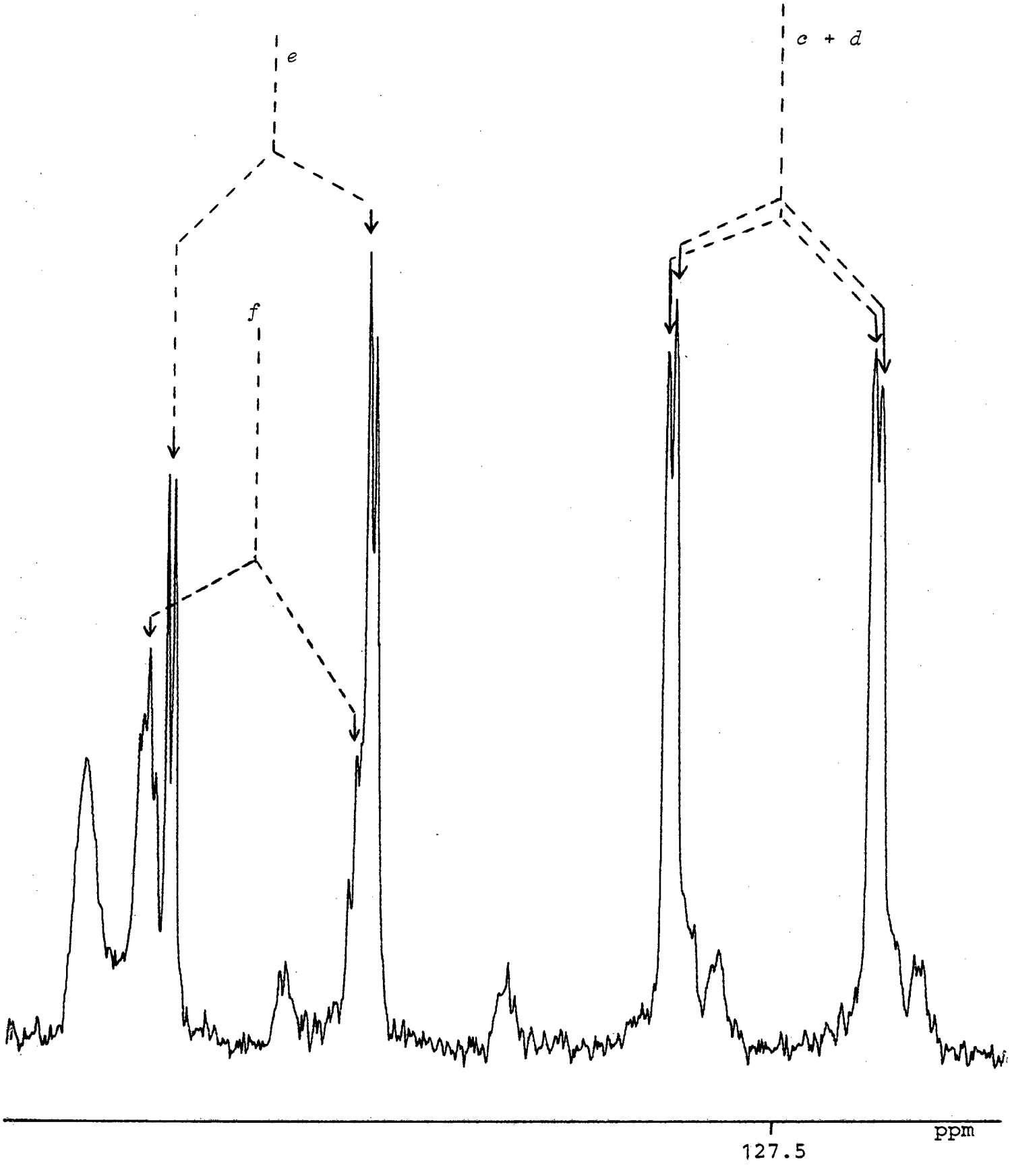


Fully coupled spectrum of A
(low field region)

Fully coupled spectrum of 4.1 (high field region)



Fully coupled spectrum of 4.1 (low field region)



APPENDIX II Observed and Calculated Structure Factors (FO and FC respectively) for Dimethyl-(quinolin-8-yl) phosphate

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
1	0	0	7	8	10	4	0	20	20	-4	2	1	28	30	-2	4	1	15	14	-6	6	1	8	-8
2	0	0	68	-70	12	4	0	14	-14	-3	2	1	17	-19	-1	4	1	44	-44	-4	6	1	8	7
3	0	0	91	92	1	5	0	8	9	-2	2	1	25	-25	0	4	1	52	52	-3	6	1	10	-10
5	0	0	34	-34	2	5	0	38	-38	-1	2	1	12	-10	1	4	1	13	11	-2	6	1	8	-8
6	0	0	26	26	4	5	0	19	20	0	2	1	104	-106	2	4	1	37	-37	0	6	1	6	-6
8	0	0	26	-27	5	5	0	28	-29	1	2	1	78	78	3	4	1	7	7	2	6	1	7	7
9	0	0	46	45	6	5	0	8	-9	2	2	1	42	42	5	4	1	8	-8	-14	0	2	7	-6
10	0	0	16	-16	7	5	0	25	25	3	2	1	48	-49	6	4	1	8	8	-13	0	2	10	10
12	0	0	23	24	8	5	0	7	-8	4	2	1	31	29	7	4	1	14	14	-12	0	2	14	15
13	0	0	6	-4	10	5	0	8	9	5	2	1	35	36	8	4	1	14	-14	-11	0	2	22	-22
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3	1	0	33	-33	4	6	0	20	-19	9	2	1	27	-28	-11	5	1	8	-7	-7	0	2	30	30
4	1	0	6	6	5	6	0	10	-10	11	2	1	7	4	-7	5	1	12	13	-6	0	2	27	-26
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7	1	0	25	-25	9	6	0	7	7	-12	3	1	24	-24	2	5	1	17	17	-3	0	2	23	-24
8	1	0	28	29	10	6	0	10	-9	-11	3	1	15	13	3	5	1	7	-7	-2	0	2	142	-143
9	1	0	15	-14	2	7	0	5	4	-9	3	1	25	-26	-10	6	1	9	-9	-1	0	2	10	9
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11	1	0	24	24	-12	1	1	14	14	-7	3	1	10	-10	-7	6	1	10	-10	1	0	2	51	-52
0	2	0	148	-149	-11	1	1	4	-4	-6	3	1	30	-29	-6	6	1	11	11	2	0	2	4	-3
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8	3	0	10	9	4	1	1	27	-28	11	3	1	10	-10	-7	7	1	9	-9	-6	1	2	12	-12
12	3	0	8	-10	5	1	1	28	-26	12	3	1	8	-8	-6	7	1	7	7	-5	1	2	31	30
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8	4	0	5	5	-9	2	1	14	-15	-4	4	1	24	-24	7	7	1	13	-12	6	1	2	21	-20
9	4	0	10	-9	-7	2	1	33	33	-3	4	1	28	29	8	7	1	7	6	7	1	2	16	16

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
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9	1	2	22	-22	-2	4	2	4	5	-2	8	2	5	-5	-6	3	3	24	24	-5	6	3	26	-26
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7	3	2	8	8	1	6	2	10	11	6	2	3	6	-7	-5	5	3	19	19	-3	0	4	54	-53
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9	3	2	7	-6	4	6	2	20	-20	8	2	3	9	-9	0	5	3	17	-18	-1	0	4	98	95
10	3	2	9	10	5	6	2	4	4	9	2	3	10	-10	1	5	3	14	-14	0	0	4	12	11
-12	4	2	13	-14	6	6	2	5	5	10	2	3	17	17	3	5	3	7	-	1	0	4	29	28
-11	4	2	9	-10	7	6	2	6	-6	11	2	3	7	-8	5	5	3	4	-3	2	0	4	8	8
-10	4	2	12	-12	-9	7	2	4	-5	12	2	3	11	-11	6	5	3	8	8	3	0	4	9	-8
-8	4	2	19	19	-6	7	2	9	-9	-13	3	3	7	-7	-11	6	3	4	-3	4	0	4	36	30
-7	4	2	12	-12	-4	7	2	9	8	-12	3	3	10	-10	-10	6	3	4	-4	6	0	4	12	-13
-6	4	2	9	-8	-1	7	2	5	-5	-10	3	3	19	-20	-9	6	3	5	-2	7	0	4	16	-16
-5	4	2	37	37	5	7	2	8	-9	-8	3	3	6	6	-6	6	3	6	-6	8	0	4	13	13

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
-9	0	4	6	-6	-5	3	4	16	16	6	6	4	9	-9	5	2	5	13	14	-2	5	5	14	-14
12	0	4	7	-8	-1	3	4	9	-9	-6	7	4	7	-5	6	2	5	11	10	-1	5	5	9	8
-13	1	4	9	-9	0	3	4	12	-12	-5	7	4	7	-8	7	2	5	12	13	1	5	5	7	-7
-12	1	4	45	-45	1	3	4	9	-9	-2	7	4	8	-6	8	2	5	15	-14	2	5	5	5	-5
-10	1	4	8	8	2	3	4	5	-5	0	7	4	5	5	9	2	5	7	6	3	5	5	8	8
-9	1	4	11	-12	3	3	4	3	-4	1	7	4	7	-7	10	2	5	8	8	4	5	5	10	-11
-7	1	4	20	-19	4	3	4	26	25	2	7	4	11	-11	-15	3	5	10	9	5	5	5	9	-9
-6	1	4	11	11	5	3	4	18	19	3	7	4	5	7	-12	3	5	19	19	-8	6	5	5	-5
-5	1	4	45	-42	6	3	4	11	11	4	7	4	10	9	-11	3	5	10	-10	-7	6	5	8	8
-4	1	4	10	-11	8	3	4	7	-7	-3	8	4	4	-3	-10	3	5	25	-25	-5	6	5	12	-12
-3	1	4	26	-25	9	3	4	6	6	1	8	4	12	12	-9	3	5	16	16	-4	6	5	15	17
-2	1	4	12	12	11	3	4	10	-9	-13	1	5	5	-4	-8	3	5	12	-12	-2	6	5	14	-14
-1	1	4	8	-7	-12	4	4	9	9	-12	1	5	13	-12	-7	3	5	4	-3	0	6	5	12	13
0	1	4	54	-53	-10	4	4	7	-7	-11	1	5	19	18	-6	3	5	16	16	3	6	5	8	9
1	1	4	15	15	-9	4	4	17	17	-10	1	5	12	12	-5	3	5	22	21	6	6	5	4	-5
2	1	4	27	-28	-7	4	4	26	-27	-9	1	5	22	-22	-4	3	5	11	-11	-6	7	5	12	-13
3	1	4	29	29	-6	4	4	13	14	-8	1	5	24	24	-3	3	5	17	18	-5	7	5	8	8
4	1	4	10	-9	-5	4	4	13	14	-7	1	5	10	10	-2	3	5	17	16	-4	7	5	4	5
5	1	4	22	-22	-1	4	4	37	34	-6	1	5	30	-29	-1	3	5	9	8	-3	7	5	12	-12
6	1	4	6	-7	0	4	4	42	42	-5	1	5	11	-11	0	3	5	27	26	0	7	5	14	-15
7	1	4	13	13	1	4	4	18	-17	-4	1	5	14	14	1	3	5	25	-26	1	7	5	7	6
9	1	4	14	-14	2	4	4	15	-16	-3	1	5	35	-35	2	3	5	9	9	4	7	5	15	16
10	1	4	15	15	3	4	4	13	14	-2	1	5	7	7	4	3	5	17	-17	-6	8	5	7	-9
12	1	4	4	2	4	4	4	9	-8	0	1	5	51	-50	6	3	5	24	25	-4	8	5	4	-4
-13	2	4	7	-7	6	4	4	26	26	1	1	5	22	22	8	3	5	5	-4	2	8	5	10	-11
-12	2	4	7	-6	9	4	4	12	12	2	1	5	18	19	9	3	5	14	14	-16	0	6	5	-4
-11	2	4	7	-7	10	4	4	6	-5	3	1	5	9	-9	10	3	5	13	-12	-15	0	6	13	-13
-10	2	4	26	-26	-11	5	4	7	-7	5	1	5	14	14	-12	4	5	7	7	-12	0	6	43	-44
-7	2	4	29	28	-10	5	4	7	7	6	1	5	13	-14	-10	4	5	14	13	-9	0	6	18	-19
-5	2	4	11	-10	-8	5	4	26	-26	9	1	5	6	-6	-9	4	5	9	-9	-8	0	6	35	33
-4	2	4	12	11	-7	5	4	4	4	10	1	5	7	5	-8	4	5	4	-5	-6	0	6	35	-33
-3	2	4	5	-4	-6	5	4	10	11	-15	2	5	4	-4	-7	4	5	9	9	-5	0	6	14	15
-2	2	4	21	20	-5	5	4	14	-14	-14	2	5	7	6	-6	4	5	13	-13	-4	0	6	3	6
-1	2	4	39	-38	-3	5	4	8	8	-13	2	5	5	-5	-5	4	5	7	-6	-3	0	6	85	-86
0	2	4	23	-22	-2	5	4	15	-16	-12	2	5	23	-23	-4	4	5	12	13	-2	0	6	27	25
1	2	4	21	-21	-1	5	4	22	22	-10	2	5	11	-10	-3	4	5	14	15	-1	0	6	23	-23
2	2	4	10	10	0	5	4	29	28	-8	2	5	11	12	-2	4	5	30	-31	0	0	6	73	-71
3	2	4	5	5	1	5	4	14	-14	-7	2	5	11	10	-1	4	5	15	15	1	0	6	12	14
4	2	4	20	-19	2	5	4	12	12	-6	2	5	10	9	0	4	5	9	9	2	0	6	6	-7
5	2	4	6	6	3	5	4	14	15	-5	2	5	4	-4	1	4	5	11	-11	3	0	6	18	-18
8	2	4	5	-6	4	5	4	27	-28	-4	2	5	4	4	2	4	5	7	7	4	0	6	39	37
-14	3	4	6	5	5	5	4	25	-26	-3	2	5	16	-15	3	4	5	4	-4	6	0	6	45	-45
-13	3	4	5	5	-9	6	4	9	-9	-2	2	5	28	27	4	4	5	16	-18	9	0	6	8	-9
-11	3	4	7	7	-7	6	4	8	9	-1	2	5	37	-36	5	4	5	10	-11	10	0	6	8	6
-10	3	4	8	8	-6	6	4	6	-5	0	2	5	13	-12	7	4	5	11	-12	-16	1	6	6	-6
-9	3	4	5	-6	-1	6	4	10	-11	2	2	5	12	-13	-11	5	5	5	-6	-15	1	6	10	-9
-8	3	4	10	10	0	6	4	32	-32	3	2	5	5	5	-7	5	5	9	-9	-11	1	6	8	8
-7	3	4	22	21	2	6	4	13	13	4	2	5	14	14	-5	5	5	8	-6	-10	1	6	18	-19

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
-9	1	6	11	12	6	3	6	11	12	-8	7	6	7	7	-8	3	7	23	-21	-4	7	7	9	-8
-7	1	6	16	14		3	6	10	-10	-6	7	6	13	-13	-7	3	7	13	12	-2	7	7	7	6
-6	1	6	56	54	8	3	6	8	-8	0	7	6	10	11	-6	3	7	10	10	1	7	7	5	5
-5	1	6	36	37	9	3	6	7	8	1	7	6	5	4	-5	3	7	8	-8	2	7	7	7	-7
-4	1	6	32	-34	-12	4	6	8	7	-13	1	7	11	-11	-4	3	7	20	19	-16	0	8	14	-12
-3	1	6	9	-8	-11	4	6	26	-26	-12	1	7	9	-10	-3	3	7	14	14	-15	0	8	7	5
-2	1	6	54	53	-10	4	6	15	-15	-11	1	7	12	12	-2	3	7	23	-22	-14	0	8	5	5
-1	1	6	13	-14	-9	4	6	12	12	-10	1	7	10	-10	-1	3	7	27	25	-13	0	8	16	-16
0	1	6	19	-18	-8	4	6	14	-14	-8	1	7	27	26	0	3	7	17	17	-11	0	8	20	19
1	1	6	22	-23	-7	4	6	10	-11	-7	1	7	10	-11	1	3	7	19	-20	-10	0	8	21	-21
2	1	6	4	-5	-6	4	6	27	27	-6	1	7	9	-9	2	3	7	20	21	-9	0	8	37	37
3	1	6	20	20	-3	4	6	9	10	-5	1	7	17	18	4	3	7	31	-30	-8	0	8	14	15
4	1	6	15	16	-2	4	6	22	-22	-4	1	7	29	-30	7	7	7	9	-8	-7	0	8	46	-48
5	1	6	10	10	-1	4	6	17	16	-3	1	7	17	-16	8	3	7	11	11	-6	0	8	32	32
6	1	6	26	29	0	4	6	10	10	-2	1	7	39	36	-13	4	7	5	6	-5	0	8	27	26
7	1	6	13	12	1	4	6	28	-29	-1	1	7	23	-23	-12	4	7	7	-9	-4	0	8	39	-38
8	1	6	8	-8	3	4	6	15	16	0	1	7	35	-35	-10	4	7	14	14	-3	0	8	18	19
-9	1	6	9	9	4	4	6	22	-23	1	1	7	29	29	-9	4	7	15	-16	-2	0	8	42	42
-15	2	6	6	7	5	4	6	12	-13	3	1	7	14	-14	-7	4	7	8	8	-1	0	8	24	-24
-12	2	6	23	24	7	4	6	11	-11	4	1	7	18	18	-6	4	7	18	-18	0	0	8	8	10
-11	2	6	16	17	8	4	6	9	10	5	1	7	8	8	-5	4	7	5	-4	1	0	8	18	18
-9	2	6	6	7	-13	5	6	7	8	-15	2	7	10	9	-4	4	7	15	16	2	0	8	29	-30
-8	2	6	10	-10	-11	5	6	12	-12	-13	2	7	10	-11	-3	4	7	13	-14	3	0	8	17	17
-5	2	6	19	18	-10	5	6	18	18	-12	2	7	11	10	-2	4	7	12	-12	4	0	8	17	17
-3	2	6	9	10	-9	5	6	14	-14	-11	2	7	9	-10	-1	4	7	9	10	5	0	8	18	18
-2	2	6	9	8	-8	5	6	11	-11	-10	2	7	25	-26	0	4	7	18	-18	6	0	8	16	16
-1	2	6	19	15	-7	5	6	19	-18	-9	2	7	25	24	2	4	7	14	14	-15	1	6	11	12
0	2	6	19	21	-4	5	6	18	18	-8	2	7	4	-3	3	4	7	5	-5	-13	1	8	8	-9
1	2	6	9	8	-3	5	6	18	-18	-7	2	7	9	-10	6	4	7	8	-8	-12	1	6	12	11
2	2	6	21	21	-1	5	6	23	23	-6	2	7	30	38	-10	5	7	9	-10	-11	1	8	15	-15
3	2	6	9	-9	0	5	6	16	-17	-4	2	7	9	-8	-7	5	7	14	-14	-10	1	8	7	-6
4	2	6	11	-11	1	5	6	13	-13	-3	2	7	26	26	-3	5	7	9	-9	-9	1	8	22	22
5	2	6	15	16	2	5	6	17	18	-2	2	7	5	-6	0	5	7	5	-6	-8	1	8	33	-34
6	2	6	21	21	3	5	6	8	9	0	2	7	26	25	2	5	7	5	-3	-7	1	8	9	9
10	2	6	8	-7	5	5	6	6	6	1	2	7	22	-23	-11	6	7	12	13	-6	1	8	19	19
-12	3	6	9	-10	6	5	6	8	-8	2	2	7	11	-11	-9	6	7	9	-9	-5	1	8	24	-25
-11	3	6	8	-9	-11	6	6	10	10	3	2	7	19	20	-8	6	7	6	7	-4	1	8	5	-4
-8	3	6	4	6	-10	6	6	6	6	4	2	7	26	-27	-6	6	7	28	-28	-3	1	8	24	24
-7	3	6	10	-10	-8	6	6	6	5	6	2	7	34	33	-4	6	7	12	12	-2	1	8	9	-9
-6	3	6	14	-14	-7	6	6	5	-3	7	2	7	10	-10	-3	6	7	14	-14	-1	1	8	11	10
-5	3	6	8	-8	-6	6	6	14	-14	8	2	7	6	-5	-2	6	7	7	6	0	1	8	35	32
-3	3	6	11	11	-3	6	6	5	-6	9	2	7	14	14	-1	6	7	6	6	1	1	8	34	-36
-2	3	6	24	-24	-2	6	6	12	12	-15	3	7	6	6	0	6	7	5	-6	2	1	8	20	21
-1	3	6	5	5	-1	6	6	6	-5	-13	3	7	9	9	1	6	7	4	5	3	1	8	12	12
0	3	6	12	12	0	6	6	11	-10	-12	3	7	20	21	3	6	7	8	-9	4	1	8	44	-45
1	3	6	6	-7	1	6	6	10	10	-11	3	7	10	-10	-8	7	7	15	15	6	1	8	17	17
4	3	6	18	-18	4	6	6	9	9	-10	3	7	8	7	-6	7	7	5	-5	7	1	8	6	-5
5	3	6	15	-15	5	6	6	5	6	-9	3	7	7	8	-5	7	7	5	5	-11	2	8	13	-14

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
-9	2	8	9	-10	-12	5	8	13	-14	-11	2	9	27	-26	-6	5	9	9	-9	-7	2	10	19	-20
-7	2	8	15	16	-11	5	8	19	19	-10	2	9	9	8	-4	5	9	5	5	-5	2	10	8	8
-6	2	8	4	-4	-10	5	9	6	7	-9	2	9	7	7	-2	5	9	8	8	-1	2	10	13	-13
-5	2	8	8	-8	-9	5	8	17	-17	-8	2	9	25	-24	-1	5	9	8	8	0	2	10	12	-11
-3	2	8	12	13	-8	5	8	15	14	-7	2	9	24	24	0	5	9	11	12	1	2	10	15	16
-2	2	8	8	-8	-7	5	8	12	-12	-6	2	9	17	17	-8	6	9	17	16	2	2	10	6	-7
-1	2	8	8	-7	-6	5	8	37	-37	-4	2	9	20	19	-7	6	9	5	5	3	2	10	9	-10
0	2	8	15	-14	-5	5	8	8	7	-3	2	9	9	10	-6	6	9	8	-8	4	2	10	9	10
2	2	8	13	13	-4	5	8	7	-7	-2	2	9	28	-27	-5	6	9	6	6	5	2	10	10	9
3	2	8	15	-16	-3	5	8	22	-23	-1	2	9	30	29	-4	6	9	5	-5	-11	3	10	6	-6
4	2	8	6	-7	-2	5	8	23	23	0	2	9	4	3	1	6	9	8	9	-10	3	10	5	-6
5	2	8	4	-5	0	5	8	23	-24	1	2	9	23	-24	-6	7	9	12	13	-9	3	10	5	5
6	2	8	13	-14	1	5	8	15	15	2	2	9	24	25	-4	7	9	7	-8	-8	3	10	4	-3
7	2	8	5	-4	2	5	8	8	7	3	2	9	6	-6	-3	7	9	5	5	-7	3	10	21	-22
13	3	8	6	6	3	5	8	7	-8	4	2	9	21	-20	-2	7	9	11	-11	-6	3	10	16	-16
-12	3	8	6	7	4	5	8	5	5	5	2	9	8	7	-15	0	10	6	5	-4	3	10	8	7
-11	3	8	10	-10	5	5	8	8	-4	6	2	9	8	7	-11	0	10	33	-36	-3	3	10	14	-14
-10	3	8	7	-7	-10	6	8	16	-16	7	2	9	9	-8	-9	0	10	30	30	-2	3	10	5	6
-9	3	8	7	6	-6	6	8	15	15	-13	3	9	12	13	-8	0	10	29	-29	-1	3	10	11	10
-8	3	8	28	27	-4	6	8	11	-11	-10	3	9	13	14	-7	0	10	25	29	0	3	10	9	-9
-5	3	8	11	11	-3	6	8	9	8	-9	3	9	25	-24	-6	0	10	43	44	3	3	10	6	-7
-4	3	8	10	10	-2	6	8	9	8	-7	3	9	6	-6	-5	0	10	25	-27	4	3	10	11	-11
-3	3	8	11	-11	-1	6	8	12	-11	-6	3	9	21	-21	-4	0	10	15	-15	-12	4	10	10	10
-1	3	8	13	13	2	6	8	7	-8	-5	3	9	13	13	-3	0	10	26	26	-11	4	10	10	9
0	3	8	6	-7	3	6	8	6	6	-4	3	9	8	7	-2	0	10	20	-21	-9	4	10	9	-9
1	3	8	17	-18	-8	7	8	5	6	-3	3	9	19	-18	-1	0	10	6	6	-8	4	10	12	11
3	3	8	5	5	-7	7	8	10	10	-2	3	9	7	8	0	0	10	21	20	-7	4	10	7	-7
4	3	8	4	-4	-4	7	8	6	5	-1	3	9	7	6	1	0	10	22	-21	-6	4	10	23	-21
5	3	8	14	15	0	7	8	10	10	0	3	9	34	-33	2	0	10	6	7	-5	4	10	10	10
6	3	8	9	10	-15	1	9	6	5	1	3	9	18	20	3	0	10	7	8	-4	4	10	4	-3
7	3	8	8	-8	-13	1	9	8	-9	3	3	9	17	-18	4	0	10	11	-11	-3	4	10	14	-13
-13	4	8	13	13	-12	1	9	7	7	4	3	9	11	10	-13	1	10	14	15	-2	4	10	22	21
-12	4	8	7	8	-10	1	9	11	-11	6	3	9	18	-18	-12	1	10	6	8	1	4	10	7	8
-11	4	8	5	2	-9	1	9	25	25	-13	4	9	7	-8	-11	1	10	10	-11	2	4	10	5	-4
-10	4	8	14	13	-8	1	9	6	-7	-11	4	9	10	10	-10	1	10	16	17	4	4	10	9	8
-8	4	8	18	-18	-6	1	9	30	30	-10	4	9	15	-14	-9	1	10	16	-17	-11	5	10	9	9
-7	4	8	8	-7	-5	1	9	10	-10	-8	4	9	16	16	-8	1	10	10	-11	-10	5	10	10	-9
-6	4	8	11	-10	-4	1	9	22	-22	-7	4	9	28	-27	-7	1	10	25	26	-9	5	10	5	5
-5	4	8	13	13	-3	1	9	29	29	-6	4	9	15	-16	-6	1	10	24	25	8	5	10	12	12
-4	4	8	20	21	-2	1	9	5	5	-5	4	9	10	10	-5	1	10	17	16	-6	5	10	10	11
-3	4	8	20	-19	-1	1	9	20	-20	-3	4	9	15	-15	-4	1	10	11	11	-5	5	10	8	7
-1	4	8	28	27	0	1	9	13	13	-2	4	9	19	20	-1	1	10	18	18	-4	5	10	21	-21
0	4	8	4	-4	1	1	9	4	-5	-1	4	9	6	-6	0	1	10	25	-24	-2	5	10	14	14
1	4	8	5	-5	2	1	9	8	6	0	4	9	16	-17	2	1	10	15	15	-1	5	10	9	-9
2	4	8	10	11	-15	2	9	5	6	1	4	9	9	9	3	1	10	6	-6	-8	6	10	4	-3
3	4	8	7	-7	-14	2	9	8	-7	4	4	9	4	3	5	1	10	5	6	-7	6	10	7	7
6	4	8	6	-6	-13	2	9	11	11	5	4	9	5	4	-13	2	10	4	4	-6	6	10	8	9
13	5	8	7	-8	-12	2	9	13	14	-8	5	9	6	7	-11	2	10	6	7	-5	6	10	5	-4

OBSERVED AND CALCULATED STRUCTURE FACTORS :

H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FL	H	K	L	FO	FC
-3	6	10	6	7	-11	3	11	16	16	-2	0	12	10	-9	-9	5	12	11	11	-9	4	13	10	10
-7	6	11	14	-14	-10	3	11	7	-7	1	0	12	8	-8	-6	5	12	8	7	-8	4	13	5	-5
0	6	11	10	10	-8	3	11	14	14	2	0	12	6	6	-5	5	12	13	-13	-6	4	13	8	9
14	1	11	6	-7	-7	3	11	20	-20	3	0	12	6	-5	-4	5	12	9	-10	-4	4	13	5	-5
-13	1	11	8	8	-6	3	11	17	-18	-11	1	12	8	8	-3	5	12	6	6	-12	0	14	11	-11
-11	1	11	16	-17	-5	3	11	6	5	-9	1	12	13	-13	-13	1	13	5	6	-10	0	14	9	9
-10	1	11	9	9	-4	3	11	11	-10	-7	1	12	26	-28	-11	1	13	5	-5	-9	0	14	15	-16
-9	1	11	8	7	-2	3	11	15	19	-6	1	12	25	-26	-10	1	13	8	8	-6	0	14	7	-7
-8	1	11	19	-18	-1	3	11	8	-8	-5	1	12	7	7	-8	1	13	7	-8	-4	0	14	8	8
-7	1	11	16	15	1	3	11	9	9	-2	1	12	11	11	-7	1	13	7	6	-2	0	14	6	6
-6	1	11	24	24	-10	4	11	8	-8	0	1	12	20	-20	-6	1	13	4	5	-1	0	14	10	10
-5	1	11	13	-12	-9	4	11	12	12	3	1	12	9	-10	-12	2	13	7	-6	-12	1	14	9	-9
-3	1	11	10	10	-8	4	11	4	6	-12	2	12	6	-7	-11	2	13	8	8	-11	1	14	9	9
-2	1	11	9	-9	-6	4	11	6	6	-10	2	12	5	-6	-9	2	13	8	-8	-10	1	14	7	-6
4	1	11	6	-5	-4	4	11	8	-8	-8	2	12	5	5	-8	2	13	10	9	-9	1	14	5	-7
-13	2	11	11	11	0	4	11	9	9	-5	2	12	16	-17	-7	2	13	16	-17	-8	1	14	8	8
-9	2	11	10	-11	-5	5	11	4	4	-3	2	12	8	8	-6	2	13	12	-12	-2	1	14	15	14
-7	2	11	13	-14	-2	5	11	6	-6	0	2	12	6	6	-5	2	13	9	9	-2	2	14	6	-6
-6	2	11	13	-13	-7	6	11	5	-7	-6	3	12	8	9	-3	2	13	8	-8	-9	3	14	6	6
-5	2	11	23	23	-4	6	11	8	-9	-5	3	12	16	19	-2	2	13	12	14	-8	3	14	5	-7
-4	2	11	10	9	-10	0	12	12	13	-2	3	12	10	10	0	2	13	9	-9	-7	3	14	16	-16
-3	2	11	15	-15	-11	0	12	14	-15	-11	4	12	9	10	1	2	13	8	8	-6	3	14	9	-8
-2	2	11	14	15	-10	0	12	19	21	-8	4	12	4	3	-10	3	13	5	-4	-9	1	15	10	-10
-1	2	11	4	1	-8	0	12	28	-29	-7	4	12	12	-11	-9	3	13	5	5	-6	1	15	8	-8
0	2	11	19	-20	-7	0	12	14	13	-5	4	12	6	6	-5	3	13	10	-11	-8	2	15	6	4
1	2	11	4	4	-6	0	12	25	27	-4	4	12	7	-7	-1	3	13	7	-7	-7	2	15	13	-13
3	2	11	12	-12	-5	0	12	12	13	0	4	12	4	3	0	3	13	12	11	-5	2	15	5	4
-13	3	11	6	-6	-4	0	12	5	4															

APPENDIX IIIa

Kinetic runs for reaction 8.1 in D_2O

T = 298 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
18.0	9.0	0.41
41.8	24.0	1.31
84.1	37.7	2.50
115.0	46.5	3.60
136.4	50.0	4.16
160.3	54.6	4.99
183.6	55.2	5.08
254.6	63.9	7.29
300.4	68.1	8.76
422.3	75.6	12.95

$k_2 = 8.35 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9980)

T = 298 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
45.6	25.4	1.41
66.2	34.2	2.15
136.6	46.4	3.53
217.8	58.4	5.81
314.2	64.0	7.36
355.7	67.5	8.60
473.7	73.4	11.43

$k_2 = 6.35 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9983)

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
19.4	30.0	1.76
39.7	50.0	4.14
132.9	70.0	9.66
185.1	73.5	11.48
325.3	79.6	16.16
510.6	86.9	27.46

$k_2 = 1.36 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9927)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
4.5	25.5	1.42
24.0	57.5	5.60
45.3	67.3	8.52
91.0	77.5	14.26
112.5	78.3	14.94
133.0	80.4	16.99
178.5	85.4	24.22
202.0	87.0	27.71

$k_2 = 3.46 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9936)

T = 338 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.0	36.0	2.33
4.5	57.9	5.70
6.8	64.3	7.46
45.0	79.5	20.96
68.8	83.5	22.92
168.2	93.4	55.01

$k_2 = 8.40 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9942)

Kinetic runs for reaction 8.1 in CD_3OD

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
111.7	10.6	0.49
132.9	13.6	0.65
185.1	17.0	0.85
325.3	26.0	1.46
442.3	30.9	1.83
510.6	35.5	2.28
609.3	39.6	2.72

$k_2 = 0.12 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9976)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
23.0	11.0	0.51
39.3	13.9	0.67
60.8	18.1	0.92
84.5	20.1	1.04
273.0	48.4	3.90
319.1	51.8	4.45
362.1	54.0	4.86
384.1	56.3	5.34

$k_2 = 0.38 \times 10^{-5} M^{-1}s^{-1}$ (r = 0.9986)

T = 338 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
24.0	29.9	1.77
45.3	43.0	3.43
91.0	59.2	6.01
114.5	66.8	8.33
135.0	69.8	9.57
157.0	73.0	11.20

$k_2 = 1.96 \times 10^{-5} M^{-1}s^{-1}$ (r = 0.9978)

Kinetic runs for reaction 8.1 in absence of solvent

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
47.0	9.4	0.02
69.0	20.7	0.05
90.3	24.1	0.06
136.4	37.3	0.12
157.9	43.6	0.15
178.9	49.3	0.19
201.2	52.3	0.22
223.4	57.9	0.27

$k_2 = 3.81 \times 10^{-7} M^{-1} s^{-1}$ (r = 0.9916)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
22.0	18.5	0.05
47.0	33.4	0.10
69.0	51.2	0.21
90.3	60.4	0.30
136.4	72.7	0.53
157.9	76.7	0.65
178.9	79.2	0.75
201.2	79.7	0.77
223.4	81.4	0.86
245.7	84.9	1.11

$k_2 = 1.27 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9920)

T = 338 K

Time (hours)	% reaction	$\frac{x}{a_o(a_0-x)}$
3.0	14.5	0.03
6.0	31.1	0.09
7.8	35.8	0.11
13.8	57.7	0.27
16.8	66.3	0.39
21.3	73.4	0.54

$k_2 = 7.79 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9915)

Kinetic run for reaction 8.1 in CD_3CN

T = 338 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
43.6	8.5	0.39
114.9	12.5	0.59
161.9	23.5	1.27
207.7	27.2	1.55
278.0	37.0	2.43
350.1	42.1	3.01

$k_2 = 2.53 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9874)

APPENDIX IIIb

Kinetic runs for reaction 8.2 in D_2O

T = 298 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
3.0	6.8	0.30
6.0	13.8	0.67
10.0	15.8	0.78
15.6	24.3	1.34
19.0	28.0	1.62
24.5	33.3	2.08
30.0	36.5	2.40
38.0	40.4	2.83
48.0	45.9	3.54
65.3	51.1	4.36
89.0	60.0	6.25

$k_2 = 1.85 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9971)

T = 298 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
3.0	9.8	0.45
6.0	16.7	0.83
10.0	24.3	1.34
12.5	25.9	1.45
15.5	32.4	1.99
20.0	36.7	2.42
48.3	49.3	4.00
70.0	58.8	5.9
95.0	64.0	7.4
146.0	75.0	10.7

$k_2 = 1.96 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9970)

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.5	12.2	0.58
4.5	19.2	0.99
7.0	25.7	1.44
10.0	32.4	2.00
14.0	41.7	2.98
18.0	45.7	3.51
23.50	54.8	5.05
27.0	56.7	5.30
32.1	59.9	6.24
38.2	61.7	6.73
46.0	67.1	8.51
54.9	71.6	10.50
64.0	74.4	12.15

$k_2 = 5.14 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9979)

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.0	10.7	0.50
4.0	20.8	1.09
6.0	29.1	1.71
10.0	38.8	2.64
12.5	43.8	3.24
14.5	47.6	3.78
16.5	49.2	4.04
20.0	52.8	4.67
26.0	60.2	6.31
30.0	61.9	6.77
37.5	66.7	8.35

$k_2 = 6.07 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9971)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
1.7	16.9	0.85
3.0	27.6	1.59
4.0	32.5	2.01
5.5	38.1	2.56
7.0	44.7	3.37
8.3	45.7	3.51
9.7	50.9	4.32
11.8	54.8	5.05
15.2	58.9	5.98
21.0	65.0	7.74
40.6	75.7	12.99
49.0	80.0	16.62

$k_2 = 8.76 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9970)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.5	21.9	1.17
3.5	30.8	1.85
4.5	35.0	2.24
6.0	42.3	3.05
7.5	46.2	3.57
10.1	54.1	4.90
12.0	58.7	5.92
16.0	64.2	7.46
20.0	67.6	8.69
24.0	69.6	9.53
29.0	74.0	11.86

$k_2 = 10.92 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9947)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
1.0	30.6	1.83
1.75	41.6	2.97
2.25	47.4	3.75
2.75	52.8	4.67
3.25	58.9	5.98
4.5	64.2	7.46
5.0	66.3	8.19

$k_2 = 45.02 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9957)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
1.0	30.8	1.85
2.0	46.9	3.68
2.5	51.3	4.39
3.0	54.4	4.97
3.75	61.0	6.51
4.75	65.9	8.13
5.5	68.9	9.24
6.5	71.9	10.63
8.0	73.6	11.66

$k_2 = 40.59 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9922)

Kinetic runs for reaction 8.2 in CD_3OD

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
10.0	7.7	0.35
18.0	12.1	0.57
38.0	21.4	1.14
62.0	29.0	1.70
86.0	36.5	2.40
110.0	41.0	2.90
180.0	52.6	4.63
234.0	58.4	5.84
353.0	71.0	10.22
392.0	72.1	10.78
440.0	73.3	11.43
510.0	75.4	12.78

$k_2 = 0.71 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9967)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
10.0	11.0	0.52
15.0	17.8	0.90
19.0	20.0	1.04
26.0	24.2	1.33
33.0	26.9	1.53
57.0	40.0	2.78
82.2	49.0	4.00
113.0	54.5	5.00
136.0	60.3	6.33

$k_2 = 1.24 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9984)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
5.0	6.2	0.28
19.8	22.5	1.21
30.9	29.9	1.78
37.0	32.5	2.01
51.7	41.8	2.99
60.0	43.8	3.23
75.2	51.5	4.42
84.0	52.4	4.59
98.0	56.3	5.36
113.0	58.8	5.95
137.0	65.3	7.84
159.0	68.4	9.02

$k_2 = 1.55 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9981)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
2.2	13.5	0.65
4.0	18.2	0.93
7.0	29.6	1.75
9.0	31.6	1.92
13.0	40.0	2.77
15.3	45.7	3.51
18.0	50.0	4.17
23.0	56.3	5.37
28.5	58.8	5.96
36.5	66.8	8.37
47.2	72.5	10.96

$k_2 = 6.33 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9978)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
1.0	6.2	0.28
4.0	21.0	1.11
6.0	27.6	1.58
10.0	36.5	2.40
14.5	45.2	3.43
18.1	52.0	4.52
22.0	54.8	5.04
26.0	58.4	5.85
30.0	62.1	6.81
32.8	63.6	7.26

$k_2 = 6.08 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9985)

Kinetic runs for reaction 8.2 in CD_3CN

T = 308 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
44.0	11.6	0.55
69.5	16.3	0.81
110.0	21.6	1.15
180.0	30.1	1.79
211.3	34.3	2.18
234.0	35.5	2.29
353.0	45.4	3.47
392.0	49.1	4.02

$k_2 = 0.27 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9986)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
15.0	10.1	0.47
19.0	12.9	0.62
26.0	16.4	0.82
33.0	19.5	1.01
57.0	28.0	1.62
82.2	35.2	2.26
113.0	38.0	2.55
136.0	42.7	3.11
160.1	46.3	3.59
191.4	51.6	4.45
206.4	52.2	4.55
276.1	60.0	6.25

$k_2 = 0.59 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9979)

T = 318 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
5.0	5.5	0.24
19.8	13.5	0.65
30.9	19.2	0.99
54.4	26.5	1.50
63.0	28.1	1.63
78.1	32.4	2.00
93.8	34.2	2.17
117.8	41.5	2.96
143.0	45.5	3.48
165.0	48.4	3.91

$k_2 = 0.63 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9980)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
3.0	7.0	0.31
7.0	13.0	0.62
12.0	21.4	1.14
16.65	27.3	1.56
20.0	30.3	1.81
25.25	34.9	2.23
30.75	39.9	2.77
40.0	44.1	3.29
49.2	49.5	4.07
58.0	55.2	5.14
66.75	57.6	5.67

$k_2 = 2.33 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9984)

T = 333 K

Time (hours)	% reaction	$\frac{x}{a_o(a_o-x)}$
4.0	10.4	0.49
6.0	12.5	0.60
10.0	19.7	1.02
14.5	24.3	1.33
18.1	28.0	1.62
22.0	33.6	2.10
26.0	36.8	2.43
33.0	42.1	3.03
42.0	48.8	3.97
50.0	52.7	4.65
63.0	58.4	5.85

$k_2 = 2.55 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9996)

APPENDIX IIIc

Kinetic runs for reaction 8.1 in D_2O/CD_3OD at 298 K

Time (hours)	80 mole % D_2O		60 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
45.7	16.3	0.81	9.1	0.41
67.7	19.0	0.97		
70.7			13.0	0.62
136.4	33.5	2.09		
158.7	34.1	2.14		
217.8	42.9	3.11	21.3	1.13
314.1	49.1	3.99	28.0	1.61
355.7	53.0	4.67		
402.1			35.7	2.30
402.7	56.0	5.27		
563.7			39.2	2.67
657.7	66.7	8.29	42.9	3.11
	$k_2 = 3.41 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9989)		$k_2 = 1.22 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9927)	

Time (hours)	40 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$
45.7	11.0	0.51
70.7	12.0	0.57
314.1	21.8	1.15
355.6	24.0	1.31
402.1	25.1	1.39
473.6	26.0	1.46
731.7	34.6	2.19
$k_2 = 0.67 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9973)		

Time (hours)	20 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$
217.8	13.7	0.66
355.6	17.7	0.89
473.6	23.1	1.24
826.7	32.7	2.01
898.2	33.4	2.08
$k_2 = 0.60 \times 10^{-6} M^{-1}s^{-1}$ (r = 0.9975)		

Kinetic runs for reaction 8.1 in D_2O/CD_3CN at 298 K

Time (hours)	92 mole % D_2O		81 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
24.0	8.5	0.38		
70.0	22.0	1.17	10.0	0.46
135.0	37.5	2.48	23.0	1.24
189.0	46.4	3.58	30.0	1.77
302.2	55.6	5.19	39.5	2.71
353.7	58.5	5.84	43.2	3.15
398.5	60.0	6.21	45.5	3.46
467.0	65.5	7.86	50.0	4.14
515.4	66.7	8.29		
805.6	73.7	11.54	62.5	6.90
	$k_2 = 4.03 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9932)		$k_2 = 2.39 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9988)	

Time (hours)	66 mole % D_2O		24 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
70.0	10.0	0.46		
135.0	11.5	0.54		
189.0	21.0	1.10	5.4	0.24
302.2	25.0	1.38	9.3	0.42
353.7	28.0	1.61	12.7	0.60
398.5	34.3	2.16		
467.0	35.0	2.23	13.5	0.65
515.4	36.6	2.46	15.5	0.76
805.6	47.3	3.72	23.0	1.24
	$k_2 = 1.26 \times 10^{-6} M^{-1} s^{-1}$ (r = 0.9921)		$k_2 = 4.39 \times 10^{-7} M^{-1} s^{-1}$ (r = 0.9916)	

Kinetic runs for reaction 8.2 in D_2O/CD_3OD at 298 K

Time (hours)	80 mole % D_2O		60 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
18.0	18.1	0.92	10.7	0.50
44.5	36.5	2.40	23.3	1.27
70.0	44.5	3.34	35.3	2.27
91.0	50.0	4.17	39.2	2.68
115.0	57.4	5.60	42.5	3.08
156.0	62.5	6.94	50.0	4.17
189.4	65.0	7.74	54.2	4.93
245.0	72.0	10.73	60.0	6.25
311.8	75.0	12.50	65.3	7.85
452.0	80.9	17.62	71.1	10.24
	$k_2 = 1.06 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9975)		$k_2 = 0.63 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9960)	

Time (hours)	40 mole % D_2O		20 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
18.0	7.1	0.32	3.5	0.15
44.5	17.6	0.89	12.3	0.59
70.0	23.2	1.26	19.6	1.02
91.0	27.3	1.56	21.1	1.11
135.0	38.5	2.61	30.9	1.86
162.0	42.5	3.08	31.9	1.95
217.5	50.0	4.17	41.8	2.99
294.5	56.5	5.42	46.8	3.66
487.0	67.4	8.62	58.3	5.82
	$k_2 = 0.50 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9988)		$k_2 = 0.33 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9967)	

Kinetic runs for reaction 8.2 in D_2O/CD_3CN at 298 K

Time (hours)	92 mole % D_2O		81 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
18.0	21.1	1.11	14.3	0.70
44.5	38.0	2.55	29.2	1.72
70.0	48.9	3.99	38.6	2.62
91.0	52.2	4.54	42.3	3.05
115.0	58.2	5.79	47.7	3.80
156.0	64.6	7.61	56.8	5.49
189.4	69.2	9.38	60.2	6.31
245.0	72.0	10.74	62.9	7.07
311.8	75.3	12.80	69.7	9.61
452.0	81.3	17.95	77.0	13.92
593.0	84.9	23.46	-	
	$k_2 = 1.05 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9975)		$k_2 = 0.83 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9974)	

Time (hours)	66 mole % D_2O		24 mole % D_2O	
	% reaction	$\frac{x}{a_o(a_o-x)}$	% reaction	$\frac{x}{a_o(a_o-x)}$
18.0	1.2	0.57	7.4	0.33
44.5	21.1	1.11	19.2	0.99
70.0	29.4	1.73	22.0	1.17
91.0	34.1	2.15	29.2	1.72
115.0	39.6	2.74	32.3	1.99
156.0	47.8	3.82	38.0	2.55
189.4	52.2	4.56	42.1	3.03
245.0	55.5	5.19	59.1	6.02
311.0	60.0	6.25	64.4	7.54
452.0	72.1	10.76	-	
	$k_2 = 0.62 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9924)		$k_2 = 0.33 \times 10^{-5} M^{-1} s^{-1}$ (r = 0.9964)	

APPENDIX IIId

Kinetic run for reaction of MeI + 4DMAP in CD_3OD at 298 K

Time (hours)	% reaction	$\frac{1}{[B_o]-[A_o]} \times \ell n \frac{[A_o]([B_o]-x)}{([A_o]-x)[B_o]}$
8.0	23.4	0.39
19.8	48.0	1.00
30.0	60.0	1.44
43.4	71.0	2.02
60.0	77.5	2.85
$k_2 = 1.29 \times 10^{-5} M^{-1} s^{-1}$		(r = 0.9995)

$[A_o]$ = 0.24 M = concentration of 4DMAP at t = O

$[B_o]$ = 0.72 M = concentration of MeI at t = O

APPENDIX IV

Main ions in the mass spectra of substrates used in ch. 9. (relative intensities given as % base peak).[a]

9.1a i) m/e 142, 11%; m/e 140, 24%; m/e 117, 3%; m/e 105, 11%; m/e 104, 100%. ii) m/e 142, <1%; m/e 140, <2%; m/e 105, 50%; m/e 104, 100%; m/e 91, 45%.

9.1b i) m/e 105, 10%; m/e 104, 100%. ii) m/e 105, 16%; m/e 104, 100%; m/e 98, <3%; m/e 91, 25%.

9.1c i) m/e 140, 3%; m/e 122, 2.5%; m/e 105, 10%; m/e 104, 100%.

9.1d i) m/e 351, 3%; m/e 321, 2.5%; m/e 105, 32%; m/e 104, 100%. ii) m/e 351, <1%; m/e 247, <1%; m/e 231, 3%; m/e 139, 2.5%; m/e 105, 68%; m/e 104, 100%; m/e 91, 31%.

9.1e i) m/e 427, <2%; m/e 139, 15%; m/e 105, 32%; m/e 104, 100%; m/e 91, 9%.

9.1h ii) m/e 152, 18%; m/e 139, <2%; m/e 135, 21%; m/e 134, 82%; m/e 121, 100%; m/e 91, 15%.

9.1i ii) m/e 259, 4%; m/e 258, <1%; m/e 213, <2%; m/e 155, 5%; m/e 154, 3%; m/e 105, 84%; m/e 104, 100%; m/e 91, 38%.

9.1j ii) m/e 136, 11%; m/e 135, 6%; m/e 134, 17%; m/e 119, 32%; m/e 117, 100%;* m/e 109, 11%; m/e 101, 28%; m/e 99, 84%; m/e 81, 38%; m/e 65, 8%; m/e 29, 14%; m/e 28, 18%.

[a] i) M.S. recorded at 12.5 eV, T = 80-130°C; ii) M.S. recorded at 70 eV, T = 130-200°C.

*M.S. at 70 eV, T = 150°C: m/e 99, 100%; m/e 117, 59%

9.1k ii) 147, 24%; m/e 145, 67%; m/e 129, 25%; m/e 119, 28%; m/e 117, 95%; m/e 109, 15%; m/e 100, 27%; m/e 99, 10%; m/e 65, 9%; m/e 32, 98%; m/e 28, 100%.

$PhCH_2CH_2Cl$. M.S. at 70 eV, T = 100°C: m/e 142, 29%; m/e 140, 91%; m/e 105, 34%; m/e 104, 12%; m/e 103, 18%; m/e 100, 39%; m/e 91, 100%; m/e 77, 27%; m/e 65, 23%.

M.S. at 70 eV, T = 140°C: m/e 142, 12%; m/e 140, 39%; m/e 105, 11%; m/e 104, 9%; m/e 103, 11%; m/e 100, 19%; m/e 91, 100%; m/e 77, 20%; m/e 65, 19%.

$AnCH_2CH_2Cl$. M.S. at 70 eV, T = 200°C: m/e 172, 7%; m/e 170, 21%; m/e 135, 2.5%; m/e 134, <1%; m/e 121, 100%; m/e 91, 6%; m/e 77, 6%; m/e 65, 3%.

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