INTRA- AND INTERMOLECULAR REACTIVITY OF ORGANIC DIACYL SYSTEMS

a thesis presented to the

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in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

by

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Contents

Abstract

The mechanism of a thermal amino group transfer-fragmentation reaction yielding carboxyamides from mixed phosphoric-carboxylic anhydrides ($RO(R^1R^2N)P(O)OC(O)R^3$; $R = R^1 =$ alkyl; $R^2 = H$, alkyl, aryl; $R^3 =$ alkyl, aryl) was elucidated from structure reactivity studies using a model system, $R = R^1 = R^2 = Me$, $R^3 = Ph$. Kinetic data was obtained using ^1H nmr spectroscopy; MNDO molecular orbital and molecular mechanics calculations, and the crystal structure of N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane ($Pna2_1$; $a = 22.229(6)$ Å, $b = 7.597(2)$ Å, $c = 7.210(2)$ Å; $V = 1217.6(6)$ Å^3. Final $R = 3.08\%$ for 1037 reflections with $I(rel) > 2\sigma I(rel)$ and 157 parameters) were useful in providing additional information about the reaction mechanism.

Transfer was specific to amino groups, and occurred intramolecularly *via* an isopolar four-centre transition state. First order rate constants k_1 measured at temperatures between 45°C and 70°C, were of the order of $10^{-6}s^{-1}$, except for the cyclic system, which reacted 50 times more slowly. Only small variations ($\leqslant 4$ times) in rate were observed when different solvents, carbonyl group substituents ($R^3 = p\text{-}MeO\text{-}C_6H_4$; $p\text{-}Cl\text{-}C_6H_4$; $p\text{-}NO_2\text{-}C_6H_4$) or nitrogen substituents ($R^2 = p\text{-}MeO\text{-}C_6H_4$; $p\text{-}Cl\text{-}C_6H_4$; $p\text{-}CF_3\text{-}C_6H_4$) were involved; a reaction constant $\rho = +0.85$ ($r = 0.981$) was obtained for the final case.

Mixed anhydrides derived from phosphorodiamidates reacted up to 12 times faster.

Activation parameters for reaction in acetone indicated specific acid-base interactions between solvent and monomeric methylmetaphosphate (the other reaction product) in the transition state; this species was identified by trapping with N-methylaniline. There was also evidence of Lewis acid catalysis by PhCOCl and I_2. MO calculations indicated an 11 kcalmol^{-1} difference in activation energy for nitrogen or oxygen transfer, as well as orbital interactions favouring carboxyamide formation. Reaction in the presence of $(CF_3CO)_2O$ indicated competitive disproportionation with substrate to give a new mixed anhydride; this system and others were investigated with respect to this alternative process.

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Conference proceedings

P(O) to C(O) shift of functional groups in mixed anhydrides; J. Symes and T.A. Modro, **Frank Warren Conference**, Hazyview, 1985.

The Quest for Metaphosphate Species. Phosphoric Chlorides and Anhydrides as Reactive Precursors; S. Cocks, J. Symes and T.A. Modro, **10th International Conference on Phoshorus Chemistry**, Bonn, 1986.

P-C Nitrogen Migration. An Insight; J. Symes, T. Modro and M. Niven, **SACI 75th Jubilee Convention**, Durban, 1987.

Mixed Phosphoric Anhydrides. Migration of Functional Groups; J. Symes and T.A. Modro, **Frank Warren Conference**, Mpekweni, 1988.

Publications

Jill Symes and Tomasz A. Modro; **Can J. Chem.**, 64, 1702 (1986). Phosphoryl to carbonyl migration of amino groups in mixed anhydrides.

S. Cocks, J. Symes, T.A. Modro; **Phosphorus and Sulphur**, 30, 229 (1987). The Quest for Metaphosphate Species. Phosphoric Chlorides and Anhydrides as Reactive Precursors.

Tomasz A. Modro, Henry S. Rzepa and Jill Symes; **J. Chem. Soc., Perkin Trans.** 2, 6, 769 (1987). The Mechanism of Phosphoryl to Carbonyl Migration of Amino Groups in Mixed Anhydrides. A MNDO - SCF Study.

J. Symes, T.A. Modro and M.L. Niven; **Phosphorus and Sulphur**, 36, 171 (1988). Phosphoryl to Carbonyl Migration of Amino Groups in Mixed Anhydrides. Reactivity and Crystal Structure of N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane.

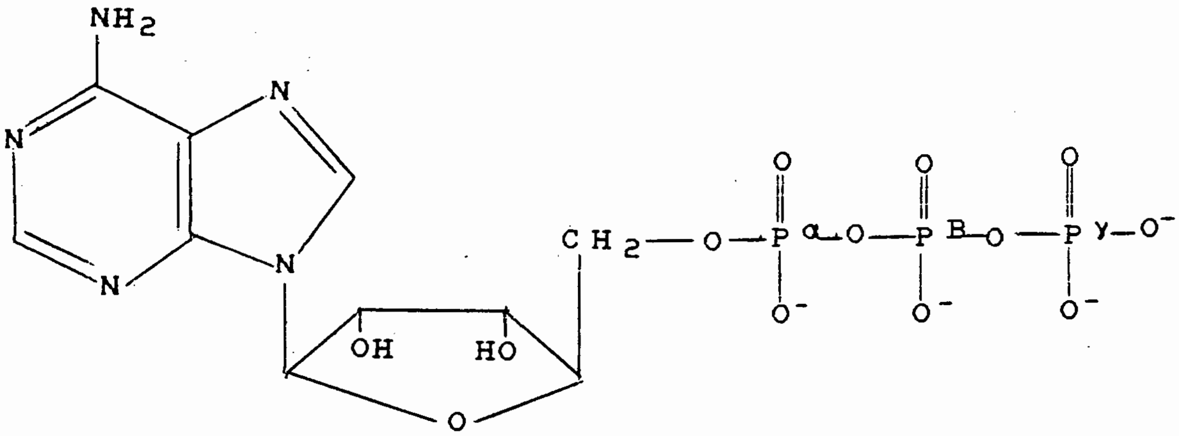
Jillian Symes and Tomasz A. Modro; **Phosphorus and Sulphur**, in press, (1988). Phosphoryl to Carbonyl Migration of Amino Groups in Mixed Anhydrides. The Effect of N-Substituents.

CHAPTER ONE

INTRODUCTION

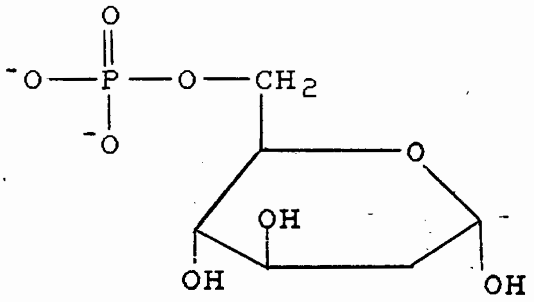
1 INTRODUCTION

The fundamental chemical processes of life are the complex reaction sequences termed "metabolic pathways": B-oxidation of fatty acids, the "energy-producing" oxidative phosphorylation process, the Citric Acid Cycle which produces carbon dioxide, the glycolysis and fermentation pathways which break down carbohydrates, as well as various biosynthetic pathways leading to the formation of amino acids and proteins, fats, nucleotides and the other building blocks of living systems. Playing a key role in all these processes are adenosine triphosphate (ATP;A̲) and the phosphorylation reaction (see Equation I).

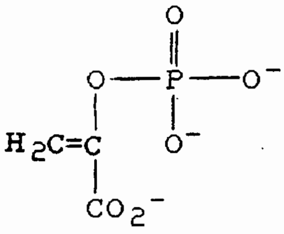


A̲

Together they result in activation of metabolic intermediates, and enable further anabolic or catabolic reactions to occur. This is possible because of the large free energy release upon cleavage of ATP, which makes attack by a nucleophile at the α,B or γ phosphorus atom favourable and so allows ready transfer of a phosphate group to that nucleophilic centre. ATP, and many other phosphorylated compounds are said to have a "high group transfer potential". Important phosphorylated intermediates are molecules such as glucose-6-phosphate (B), phosphoenol-pyruvate (C), acetylphosphate (D), carbamoyl phosphate (E), creatine phosphate (F) and the 2-deoxyribonucleotide triphosphates (e.g.G).[1]



B



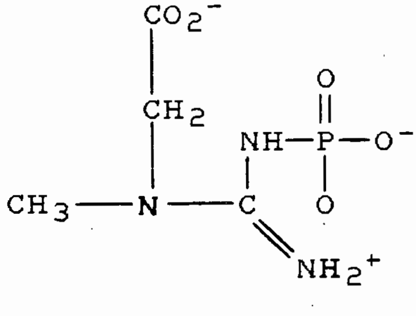
C

$MeC(O)OP(O)O_2^-$

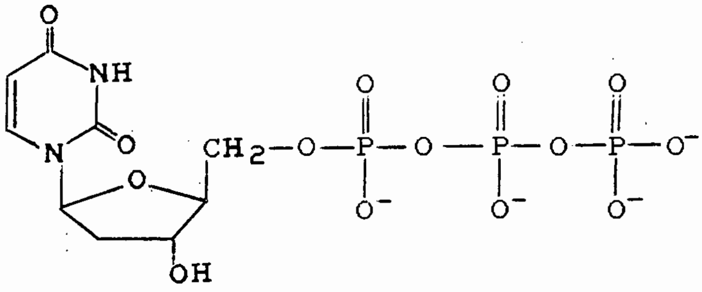
D

$HOC(O)OP(O)O_2^-$

E



F



G

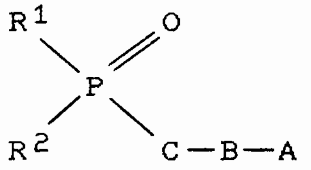
The phosphorylation reaction belongs to the general class of acylation reactions (Equation I); the acylating agent W-X-Z comprises two acyl groups derived from carboxylic, phosphoric, phosphonic, sulphonic, etc. acids, linked by oxygen, nitrogen or sulphur atoms to form the corresponding anhydride, imide or thioanhydride derivatives.

$$\text{W-X-Z} + \text{NH} \xrightarrow{\qquad} \text{W-N} + \text{Z-X-H} \qquad \text{(I)}$$

W,Z = acyl groups N = nucleophile
e.g. RC(O)-; $(RO)_2P(O)$-

X = O; S; NR

Phosphorylating agents can be described more specifically by the following structure[2]:



R^1,R^2 = aryl, alkyl, alkoxy, aryloxy, amino groups;

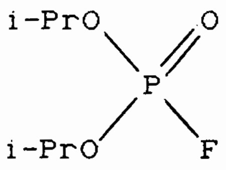
A-B-C = good leaving group

e.g. R-C(O)-O; Hal-CH_2-CH_2; $(RO)_2$-P(O)-O

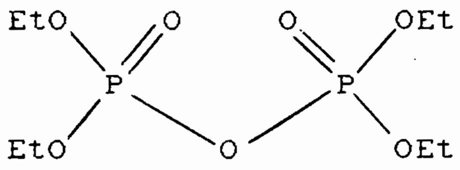
Their high group transfer potential (and that of acylating agents in general) arises from unfavourable electronic effects: the bridging atom C is subject to opposing electronwithdrawing effects and dipole-dipole interactions from the $R^1R^2P(O)$- and AB- moietes, which weaken the P-C and C-B bonds and increase the energy of the molecule. Reaction with nucleophile results in products of lower energy, without these unfavourable interactions.

The large group transfer potential of the phosphoryl group also makes phosphorylation a potentially lethal reaction:

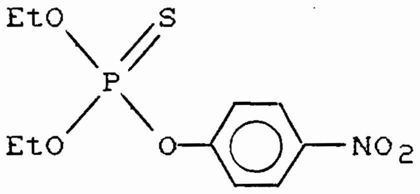
many pyrophosphate esters, phosphorofluoridates, phosphoramidates and phosphorothionates are extremely toxic, since they phosphorylate acetyl cholinesterase and prevent this enzyme from catalysing the hydrolysis of acetyl choline, a neurotransmitter; this results in the nerves being in a continual state of stimulation[3,4]. Compounds of this type have been developed as nerve gases and insecticides, and include the following:



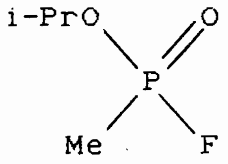
DFP



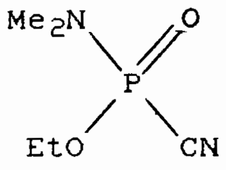
TEPP



Parathion



Sarin



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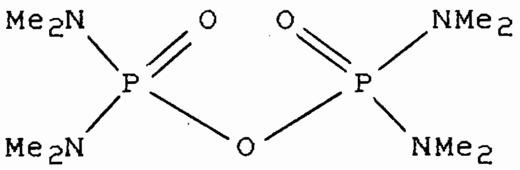
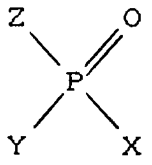


Schradan

Toxicity is usually removed upon hydrolysis, and thio-derivatives are often less toxic to mammals than the oxyanalogues, but still maintain effective insecticidal activity. Design of viable insecticides involves finding a balance between rapid activation and action in insects, and rapid hydrolysis and low toxicity in mammals.

The importance of phosphorylation and phosphorylating agents as a means both of maintaining life systems and of controlling insect lifetimes for agricultural purposes, has thus stimulated the study of organophosphorus compounds. Recent work in our laboratory has included the study of various phosphoric-carboxylic imide[5], phosphoramidate[6] and carboxyamide[7] systems, with a view to establishing the chemical and structural characters of these compounds, whilst other workers have made similar studies on acyl phosphates and phosphoroguanidines[8].

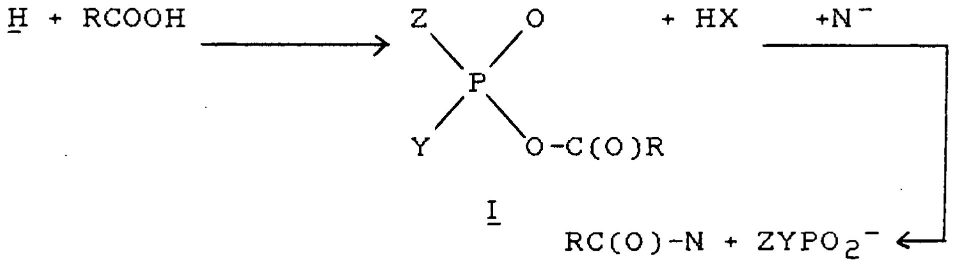
Acyl phosphates have been studied with respect to their hydrolysis[9-11], reaction with nucleophiles[12], and the effect of steric bulk and polar groups[13]. The mono- and dianions undergo hydrolysis with P-O bond cleavage and metaphosphate ion formation, but under strongly acidic or basic conditions water attacks at the carbonyl centre, and there is C-O bond cleavage. This diversity in reactivity is also reflected in the reaction of acyl phosphates with amines: primary and unhindered amines attack at the carbonyl centre, whilst tertiary amines and pyridines attack at the phosphoryl centre - and has been applied in the design[14] of carboxylic acid activating agents such as H(i-vii) for the synthesis of amides[15], anhydrides[16], esters[17] and thio esters[18], and peptides[19-21].



H

		X	Y	Z
H	i	Cl	PhNH	PhO
	ii, iii	Cl;Br	PhO	PhO
	iv, v	Cl	Cl	PhO;Me_2N
	vi	Cl	EtO	EtO
	vii	Cl	$PhCH_2O$	$PhCH_2O$

These reactions all proceed as shown in Equation II, with formation of an intermediate mixed anhydride species I.

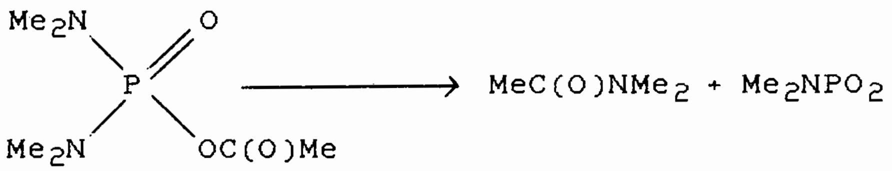


(II)

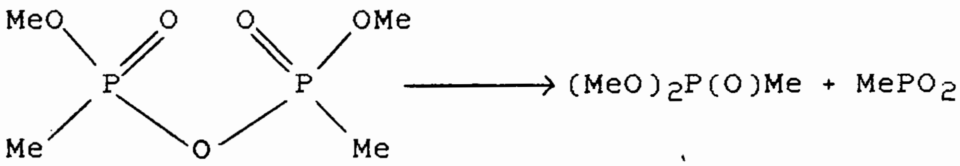
Unsymmetrical anhydrides I are known to undergo a thermal disproportionation to yield a pair of symmetrical anhydrides[19,22,23], but no mechanistic details are available. Petrov and Neimysheva employed this thermal lability of acyl phosphates in the preparation of symmetrical pyrophosphates[24] (Equation III):

$$(RO)_2P(O)Cl + R^1CO_2Ag \longrightarrow 1/2[(RO)_2PO]_2 + \\ + 1/2[R^1CO]_2O + AgCl \qquad (III)$$

but found that diamidopyrophosphates and pyrophosphinates could not be prepared in the same way. In these instances, there was further functional group transfer in either the mixed anhydride intermediate or the pyrophosphinate (Equations IV and V).

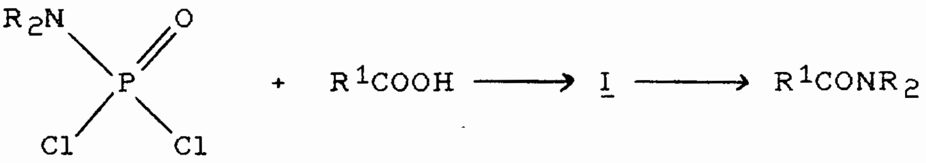


(IV)



(V)

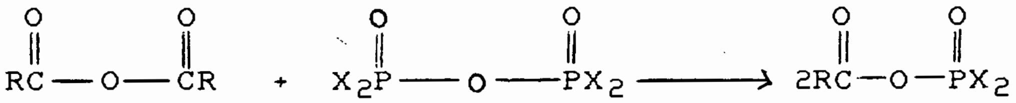
The reaction indicated in Equation IV has subsequently been used to prepare a variety of tertiary carboxyamides[25], the nitrogen moeity being supplied by N,N- dialkyl phosphoramidic dichlorides (Equation VI).



(VI)

R = Me, Et $\qquad$ R^1 = alkyl, aryl

A conproportionation reaction (essentially reverse disproportionation) has been observed[26], and results in mixed anhydride formation from two symmetrical anhydride systems (Equation VII).



$$RC(=O){-}O{-}C(=O)R + X_2P(=O){-}O{-}P(=O)X_2 \longrightarrow 2RC(=O){-}O{-}P(=O)X_2 \qquad \text{(VII)}$$

R = aryl,alkyl X = Cl,F

Distillation of the product does not yield disproportionation products (i.e. substrates), but rather acyl halides RC(O)X. (*cf*. Equation VI).

Acyl phosphates are thus versatile intermediates, and in addition to nucleophilic displacements, undergo a variety of thermal fragmentation and rearrangement reactions.

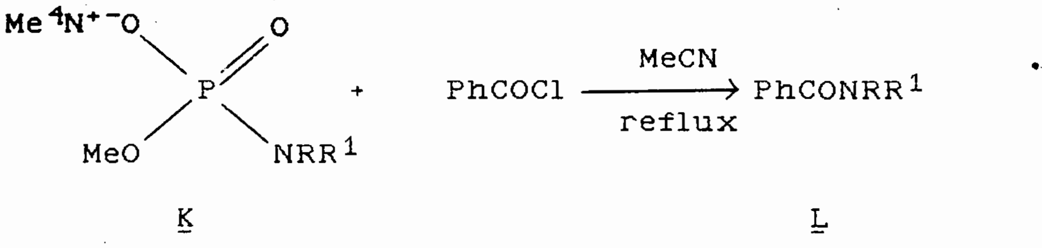
Whilst attempting the synthesis of mixed phosphoric-carboxylic imides (J̲) by N-acylation of phosphoramidates (Equation VIII), it was observed that carboxylic amides, imides and esters (R^2CONHR^1, $(R^2CO)_2NR^1$, R^2CO_2R) were also formed, and that there was significant de-ethylation during the course of reaction[5].

$$R_2P(O)NHR^1 + R^2C(O)Cl \xrightarrow{\text{base}} \underset{\underline{J}}{R_2P(O)NR^1C(O)R^2} \qquad \text{(VIII)}$$

R = MeO, EtO R^2 = Ph, Me

R^1 = Me

In order to investigate the possible role of the imide monoanion (resulting from de-ethylation) in the P-N bond cleavage process leading to amide formation, model compounds K were synthesised, and reacted under neutral conditions with benzoyl chloride (Equation IX).

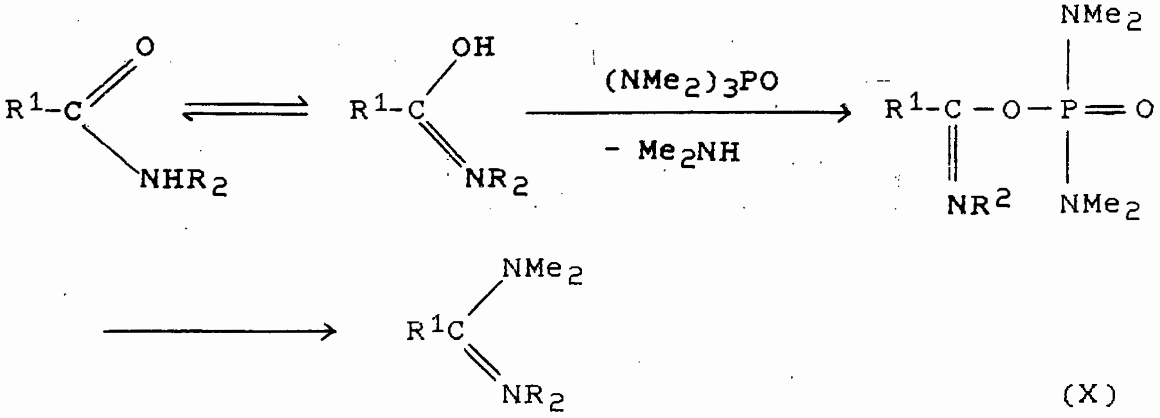


(IX)

R = Me

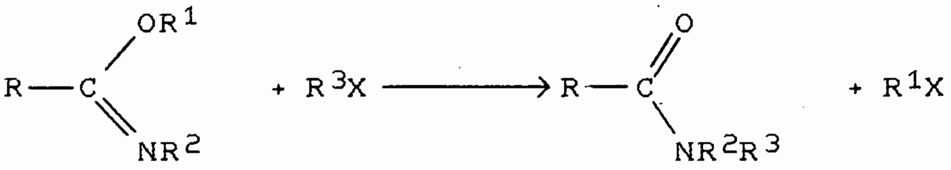
R^1 = Me, C(O)Me

Quantitative conversion of K to the carboxyamide L was observed, but no carboxylic ester formation *i.e.* there was selective transfer of amino substituents from the phosphoryl to carbonyl centre. Thermal rearrangements involving amide systems are well documented in the literature: carboxyamides have been converted to amidines in a reaction involving formation of a phosphorylated imide intermediate and subsequent transfer of a substituent from the phosphoryl to the imidyl centre (Equation X)[27]:

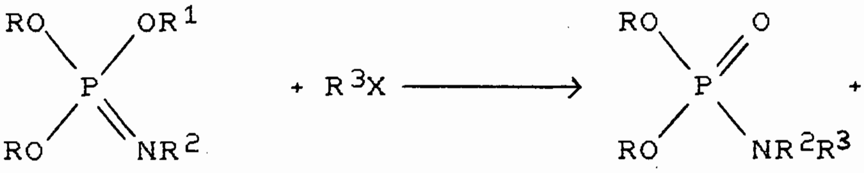


(X)

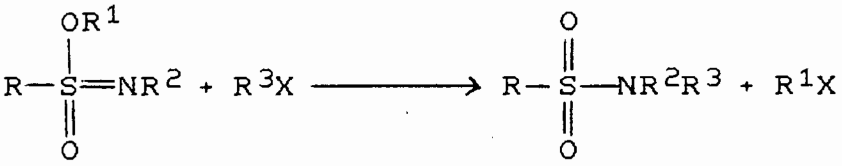
whilst the rearrangements of carboxylic[28], phosphoric[29] and sulphonic[30] imides to the isomeric (if $R^1 = R^3$) amides require the presence of electrophilic reagents such as alkyl halides (Equations XI - XIII):



(XI)



(XII)



$$R-\overset{OR^1}{\underset{O}{S}}{=}NR^2 + R^3X \longrightarrow R-\overset{O}{\underset{O}{S}}-NR^2R^3 + R^1X$$

(XIII)

and differ from the reactions indicated in Equations IX and X, in that they involve no fragmenting diacyl system, or direct attack at the acyl centre.

In view of the abovementioned diversity and interest in the chemistry of mixed diacyl systems, and in particular systems involving phosphoric and carboxylic acid derivatives, a more detailed study of the reaction between phosphoramidic acid monoester monoanions and acid chlorides (Equation IX), was planned. The aim was to establish, by means of structure-reactivity studies and chemical kinetics, a mechanism for the observed phosphoryl to carbonyl transfer of functional groups, and also to confirm and account for the apparent specificity towards nitrogen substituents.

CHAPTER TWO

PHOSPHORYL TO CARBONYL MIGRATION OF AMINO GROUPS

PHOSPHORYL TO CARBONYL MIGRATION OF AMINO GROUPS[31]

2.1 Introduction

The mechanism of a reaction is a detailed description of all the bond-making and breaking events involved in formation of the final products. Implicit in this definition is the realisation that all the steps must be chemically acceptable, and all intermediates realistic. Arriving at a satisfactory mechanism involves having undertaken a systematic investigation of the reaction in question, with the underlying philosophy being that the final hypothesis must fit the known facts. Once the mechanism is known, it becomes possible for the chemist to use this knowledge to explain other analogous processes, or to alter and modify the reaction, perhaps to obtain greater yields or make new compounds.

Thus, elucidation of a mechanism involves determining as far as possible the nature of the various intermediates, and accounting for their interconversion in terms of their structural, steric, electronic and energetic requirements. Chemical kinetics play a fundamental role in clarifying reaction mechanisms, and to this end, the influence of solvents, heat, structural variations and acid or base on the course of reaction can provide useful information[32, 33].

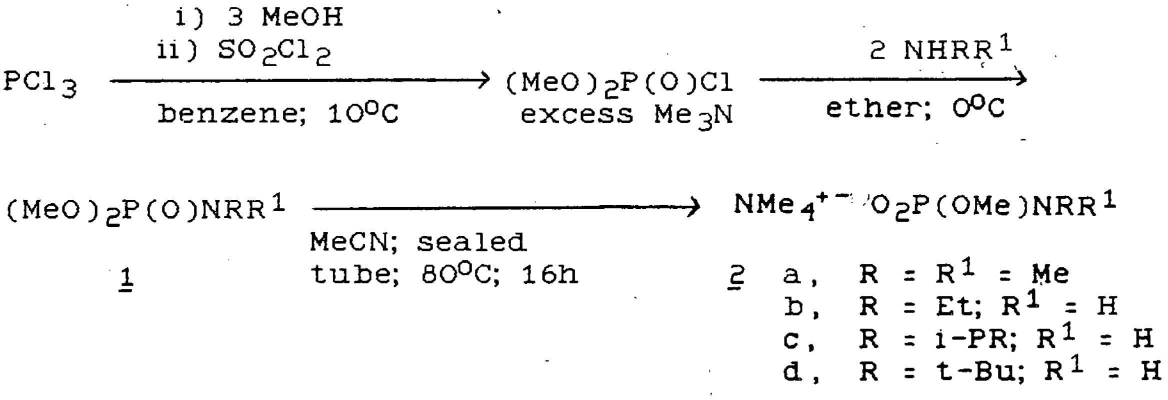
2.2 Preliminary studies

2.2.1 Generality and specificity of transfer

The evidence for nitrogen group transfer from phosphoryl to carbonyl centre obtained in our laboratory was based on reactions involving a limited number of substrates, particularly with respect to the nature of substituents at nitrogen[5]. Furthermore, for reaction between phosphoramidic acid salts and acid chlorides there was no evidence of ester group transfer to give carboxylic esters: this was surprising since, if there was collapse of the monoanion, as the weaker base and thus better leaving group, departure of alkoxy group from phosphorus would be expected to be more favourable. Ester (RO) groups are known to migrate in phosphate systems; tetramethyl- and tetraethylpyrophosphates decompose on heating to the corresponding trialkyl phosphate and alkylmetaphosphate[34], and methyl methylpyrophosphinate yields dimethyl methylphosphinate on distillation[24].

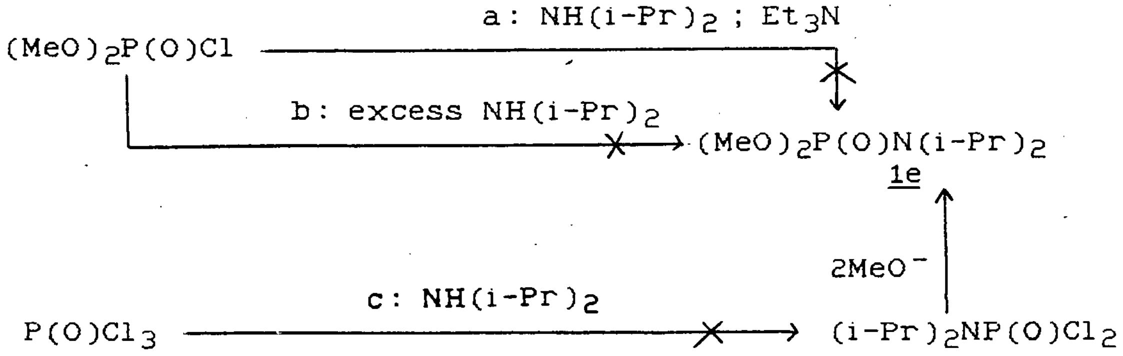
It was decided to establish firstly whether or not transfer of functional groups in the phosphoramidic acid salt - acid chloride system was specific to nitrogen moieties, and secondly, the dependence of the transfer process on the nature of substituents at nitrogen: the reaction is essentially a nucleophilic substitution at carbonyl centre, and factors which affect the nucleophilicity of the transferring group or the electrophilicity of the carbonyl centre can be expected to alter the rate, and even the specificity of the reaction.

A series of salts (2a-d) was prepared according to the reactions outlined in Scheme 1.



Scheme 1

Synthesis of the intermediate dimethyl N,N-dialkyl phosphoramidates 1 where both alkyl groups were larger than methyl proved difficult, presumably due to the increased steric bulk at nitrogen and reduction in nucleophilicity of the corresponding amine. Thus, syntheses of N,N-diisopropylphosphoramidate 1e by various methods were all unsuccessful (Scheme 2).



Scheme 2

Methods a[6b] and b[35] gave complex product mixtures arising from competing demethylation or incomplete reaction, whilst the aqueous wash required during work-up in method c[36] resulted in P-N bond cleavage; other purification methods proved unsatisfactory. Synthesis of tertiary phosphoramidate substrates 1 was thus abandoned in favour of the secondary substrates.

Salts 2 were suspended in acetonitrile and an equimolar amount of acetyl chloride added. After 4h reflux, solids were removed by vacuum filtration and solvent evaporated. The residues were examined by ^1H nmr spectroscopy. Reaction with 2a was repeated using benzoyl chloride. In all cases, all signals from substrates were absent in the final spectrum; the only identifiable compounds[37, 38] were the carboxyamides 4 arising from nitrogen group transfer (Scheme 3).

$$2 + R^2COCl \xrightarrow[\text{MeCN; 4h}]{\text{reflux}} R^2CONRR^1$$

3 a, R^2 = Ph
b, R^2 = Me

4 a, R = R^1 = Me; R^2 = Ph
b, R = Et; R^1 = H; R^2 = Me
c, R = i-Pr; R^1 = H; R^2 = Me
d, R = t-Bu; R^1 = H; R^2 = Me
e, R = R^1 = R^2 = Me

Scheme 3

No carboxylic esters were observed: methyl acetate (bp 57°C) would have been removed with solvent, but methyl benzoate (bp 200°C) would have been identified by ^1H nmr spectroscopy.

On the basis of the above reactions, it is concluded that transfer of functional groups from phosphoryl to carbonyl centre is specific to nitrogen-containing moieties; although the range of structural variations considered is small, the reaction appears to be general with respect to the nature of substituents at nitrogen and at the carbonyl centre.

2.2.2 Isolation of benzoyl methyl N,N-dimethylphosphoramidate

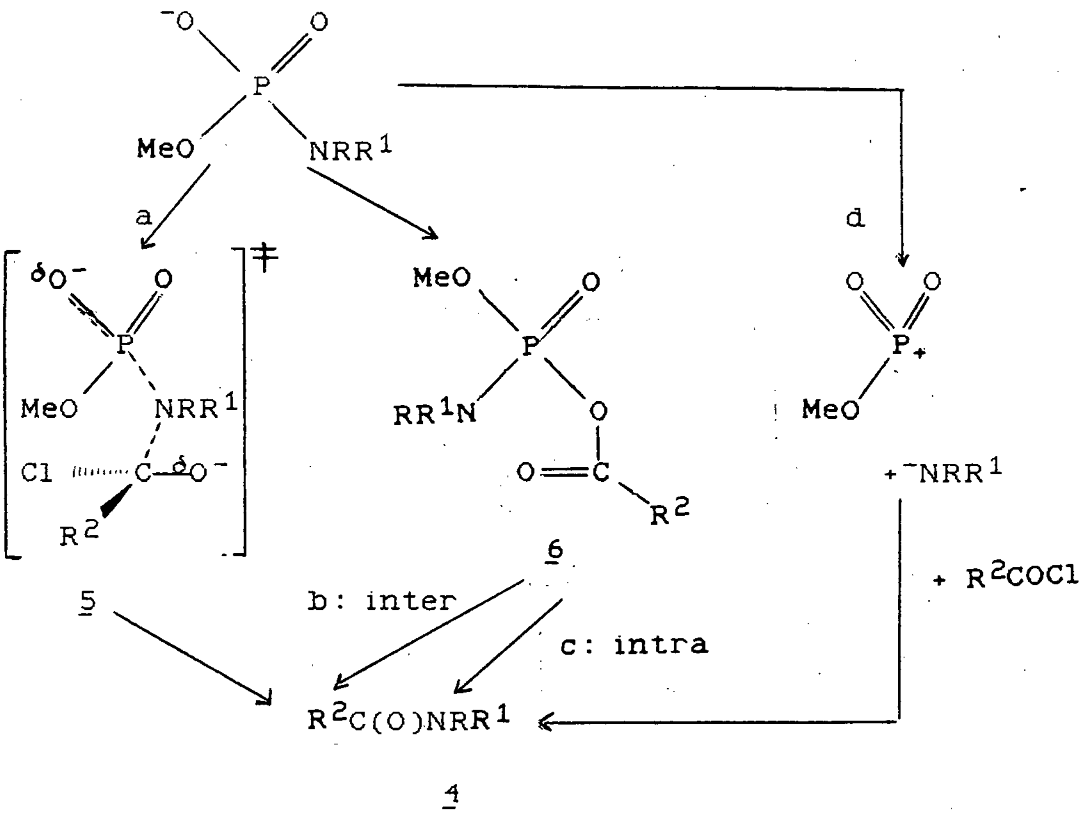
Several different pathways can be envisaged to account for the transfer of nitrogen substituents (Scheme 4):

a) charge-assisted nucleophilic substitution of acid chloride with tetrahedral transition state formation (5)[5];

b) nucleophilic substitution of acid chloride by phosphoramidate monoanion, yielding a mixed phosphoric-carboxylic anhydride 6, with subsequent transfer of the nitrogen group in an intermolecular fashion;

c) mixed anhydride formation followed by intramolecular transfer.

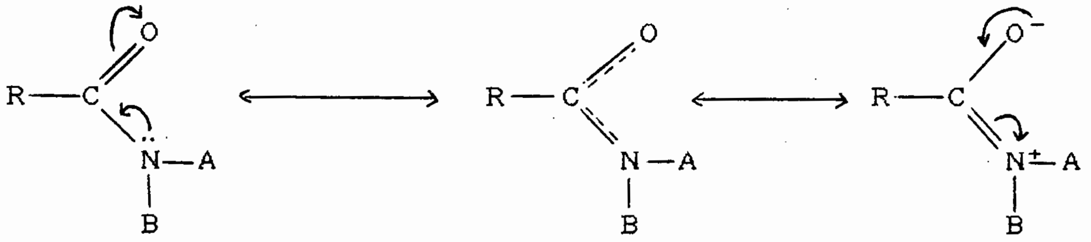
Another pathway (d), involving initial unimolecular P-N bond cleavage followed by attack at carbonyl centre appears unlikely, since when heated in the absence of acid chloride, there was no detectable P-N bond cleavage in 2a[5].



Scheme 4

The observation by Petrov and Niemysheva that phosphoramidate systems yielded only carboxyamides under conditions which resulted in the isolation of tetraalkylpyrophosphates from dialkyl phosphates (*via* initial formation of dialkyl phosphoric-carboxylic anhydrides) led us to believe that a mixed phosphoric-carboxylic anhydride system might be the intermediate in the nitrogen transfer process. Further investigations were thus aimed at demonstrating whether or not this was the case.

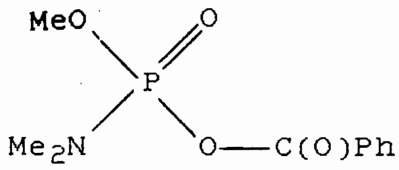
Substrates 2a and 3a were chosen as models: these compounds were readily available and gave uncomplicated ^{1}H nmr spectra. Also, the transfer product $PhCONMe_2$, 4a, could be easily identified in the ^{1}H nmr by its characteristic broad singlet in the N-methyl region, and an aromatic singlet. This pattern of signals arises because of the nature of the C-N bond in carboxyamides: the nitrogen lone pair is delocalised throughout the C(O)N bond system (Scheme 5), resulting in a planar moiety and restricted rotation about the C-N bond.



Scheme 5

The environments of the N-substituents are thus not equivalent, and at low temperatures 2 distinct signals arise[39], but coalesce at higher temperatures to give broad signals. Because of unfavourable steric interactions with the N-methyl substituents, the phenyl group in 4a is twisted out of the plane of the amide bond; the ring protons are then no longer influenced by the carbonyl group resonance effect, and become approximately equivalent.

When 3a was added to a suspension of 2a in acetonitrile at room temperature there was immediate evidence of some reaction occuring, as the solids changed from crystalline and semi-translucent in nature to a fine, white suspension. There was no further change in appearance during the course of reaction. After 3h stirring solids and solvent were removed, to yield an oil which ^1H nmr and microanalysis confirmed was the mixed anhydride benzoyl methyl N,N-dimethylphosphoramidate 6a.



6a

This anhydride is formed by simple nucleophilic substitution of chloride ion by the phosphoramidate anion (Equation 1), a process analogous to that employed by the Russian workers (Equation 2)[24].

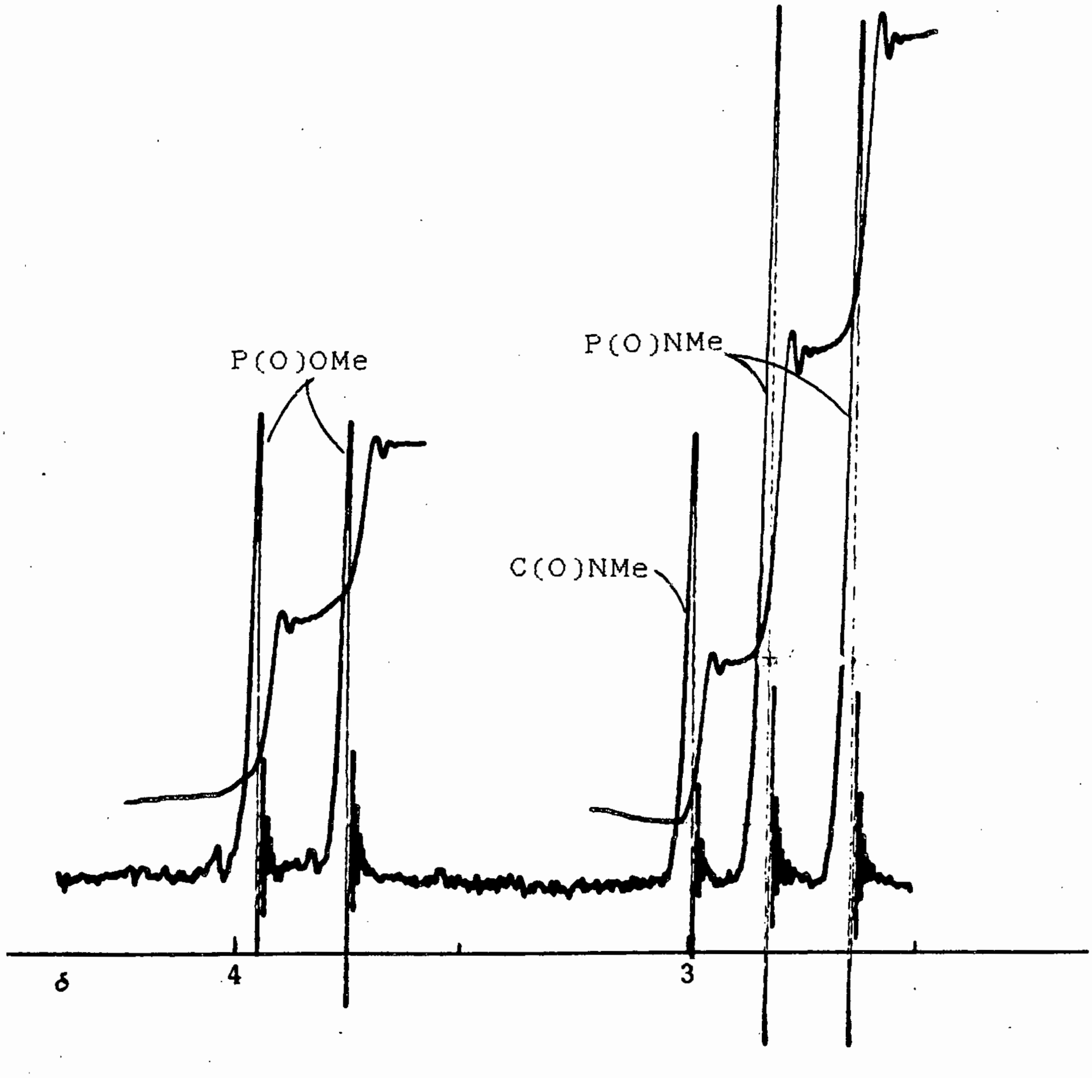
$$MeO(Me_2N)PO_2^- + PhCOCl \longrightarrow MeO(Me_2N)PO_2\text{-}C(O)Ph + Cl^- \quad (1)$$

$$(RO)_2P(O)Cl + R^1CO_2^- \longrightarrow (RO)_2PO_2C(O)R^1 + Cl^- \quad (2)$$

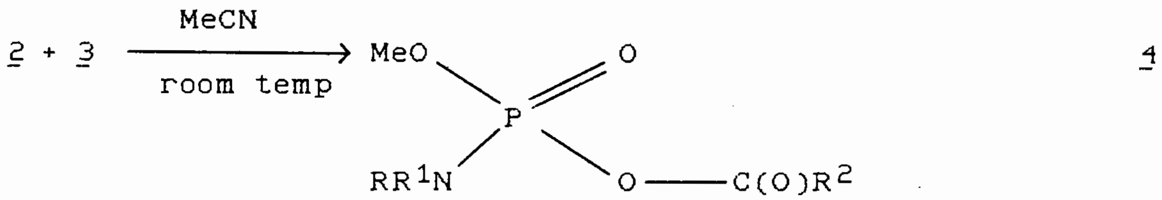
Chloride ion is precipitated as tetramethylammonium chloride; it is the formation of this salt that was seen after initiation of the reaction. Mixed anhydride formation is obviously very rapid.

When left standing at room temperature or heated in aprotic solvent 6a slowly decomposed to 4a and some polymeric phosphorus-containing species. The progress of fragmentation could be followed using ^1H nmr spectroscopy: as the intensity of the P(O)OMe and P(O)NMe$_2$ doublets diminished, and eventually disappeared, the C(O)NMe$_2$ singlet appeared and grew. The signals in the N-methyl region were clearly distinguishable, and accurate integrals could be obtained (Figure 1).

Figure 1: ^1H nmr spectrum of 6a in CCl_4 (43h; 70°C)



At this stage we concluded that the mixed anhydride 6a is the intermediate in the thermal phosphoryl to carbonyl centre transfer of amino substituents in the model system, and, by inference, that similar species 6b-e are intermediates in the other systems investigated (Scheme 6).



6 a, R = R^1 = Me; R^2 = Ph
b, R = Et; R^1 = H, R^2 = Me
c, R = i-Pr; R^1 = H; R^2 = Me
d, R = t-Bu; R^1 = H; R^2 = Me
e, R = R^1 = R^2 = Me

Scheme 6

2.3 Kinetic studies

Having established that the first step in the reaction between phosphoramidic acid salts and acid chlorides, leading to carboxyamide formation, was reaction giving a mixed phosphoric-carboxylic anhydride as intermediate, it still remained to show how the functional group transfer occurred in this molecule. The anhydride was easily synthesised, and some preliminary investigations indicated that the rate of transfer in solution was slow enough ($t_{1/2}$ > 200h; $CDCl_3$; 25°C) to enable kinetic measurements to be taken. This, coupled with the fact that anhydride 6a and product 4a could be distinguished in the ^1H nmr spectrum resulted in our choosing this technique as the primary tool for our kinetic study. The amount of carboxyamide present at any time could be calculated from the following equation.

$$X = \frac{100\ A}{A + B} \qquad (3)$$

where

X = amount of 4a, as percentage

A = increment per proton for 4a (measured from $C(O)NMe_2$ signal, δ 3.0).

B = increment per proton for 6a (measured from $P(O)NMe_2$ signal, doublet, δ 2.8).

2.3.1 Reaction order

The general features of a mechanism can often be determined from the rate law governing the reaction *i.e.* the manner in which reaction rate depends on concentration of reactants and products. In Scheme 4 it is proposed that where the intermediate 6 is involved, amino group transfer can be either uni- or bimolecular. Since reaction occurs in the absence of any other chemical species, except solvent, the reaction might be expected to obey either first or second order kinetics (Equations 4 and 5)[40].

first order: $$\frac{dx}{dt} = k_1(a_0 - x) \qquad (4a)$$

$$k_1 = {}^1\!/t \ln a_0/(a_0 - x) \qquad (4b)$$

second order:

$$\frac{dx}{dt} = k_2(a_o - x)^2 \qquad (5a)$$

$$k_2 = 1/t \, . \, x/a_o(a_o - x) \qquad (5b)$$

where

a_o = initial concentration of substrate

x = concentration of substrate or product at time t.

Solutions of 6a of known concentration in two different solvents were sealed in nmr tubes and incubated at 68°C. The extent of reaction was periodically monitored, and the amounts of 4a present at times t used in both first and second order rate laws (Equations 4b and 5b) to calculate the corresponding rate constants k_1 and k_2. The results are summarised in Table 1.

On the basis of the standard deviation for the averaged k_1 and k_2 values for each solvent it was concluded that the transfer process follows first order kinetics, and therefore has a first order dependence on the concentration of 6a. The mean of the deviations in the k_1 values obtained for both solvents is 5.4%, whilst the same value for the k_2 values is 44.4%, indicating much better fit of data to the first order rate law.

Using Ostwalds' method[41] it is possible to calculate the reaction order n from an experiment of this type (Equation 6):

Table 1: Effect of concentration on rate of formation of 4a from 6a at 68.0°C

Solvent	Expt.	[6a] (M)	10^6k_1 (s^{-1})	r	10^6k_2 ($M^{-1}s^{-1}$)	r
$(CD_3)_2CO$	1	0.182	1.95	0.994	2.43	0.993
	2	0.364	1.85	0.992	1.18	0.990
		average	1.90 ± 0.07		1.805 ± 0.88	
$CDCl_3$	3	0.187	1.49	0.994	1.86	0.988
	4	0.373	1.65	0.988	1.04	0.986
		average	1.57 ± 0.11		1.45 ± 0.58	

$$n = 1 + \frac{\log (t_{1/2})_1/(t_{1/2})_2}{\log (a_0)_2/(a_0)_1} \qquad (6)$$

where

$(t_{1/2})_1$ and $(t_{1/2})_2$ are the half-lives of Experiments 1 and 2, in which initial substrate concentrations are $(a_0)_1$ and $(a_0)_2$ respectively, and which can be calculated for first and second order reactions from the equations

$$\text{first order:} \quad t(_{1/2})_1 = \frac{\ln 2}{k_1} \qquad (7a)$$

$$\text{second order:} \quad t(_{1/2})_2 = \frac{1}{a_0 k_2} \qquad (7b)$$

Results are shown in Table 2, and confirm that reaction is first order, giving an average value of 1.04±0.17 for n from the two values calculated using k_1 values. The fact that, having used the k_2 values to calculate the second order $t_{1/2}$ terms, a value of $n=2$ was not obtained again indicates that the rate data obtained fit Equation 4 better than Equation 5.

2.3.2 Identification of products

Although we were satisfied from comparison with literature values that the product seen in the ^1H nmr spectrum was 4a, it was decided to confirm this by comparison with an authentic sample.

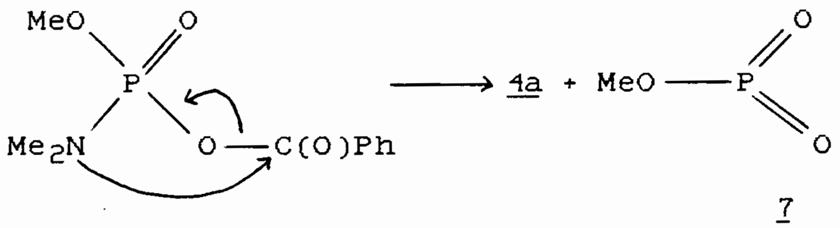
Table 2: Calculated reaction order for formation of 4a.

Expt.	a_0(M)	first order $10^{-5}(t_{1/2})_1$(s)	n	second order $10^{-6}(t_{1/2})_2$(s)	n
1	0.182	3.5		4.4	
2	0.364	3.7	0.92	4.3	1.03
3	0.187	4.7		2.9	
4	0.373	4.2	1.16	2.6	1.16

average n = 1.04 ± 0.17

4a was synthesised from $NMe_2H.HCl$ and 3a by the Schotten-Baumann method[42]. White crystals (mp 40 - 42°C) were obtained, and gave an nmr spectrum identical to that obtained from reaction mixtures. 4a was also isolated from a sample of 6a heated in acetonitrile, initially as an oil which crystallised in petroleum ether solution (mp 41 - 43°C). Microanalysis confirmed the crystals as 4a.

As nitrogen group transfer has a first order dependence on the concentration of the mixed anhydride intermediate, which contains both reacting centres, the reaction is also unimolecular, since molecularity is defined by the number of reactant molecules which come together to form a complex which directly gives rise to the products[40]. In other words, nitrogen group transfer takes place intramolecularly (with respect to the intermediate). The other product is then monomeric methylmetaphosphate 7 (Equation 8).



(8)

Species of this type, in their ionic and esterified forms, have been postulated as intermediates in a number of reactions, including the hydrolysis of phosphoric acid monoesters[43], the fragmentation of B-halophosphonates (the Conant-Swan fragmentation)[44] and (2-arylethyl)-phosphorochloridates[45], and the photolysis of 4-

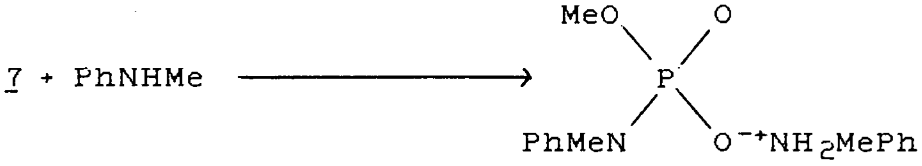
nitrobenzyl-phosphoric acid[46]. Metaphosphate ion has been proposed as an intermediate in biological phosphorylations[47] and nitrogen analogues have been implied as intermediates in the hydrolysis of phosphorodiamidochloridates[48] and in the photolysis of diaryl and dialkyl phosphinic azides[49].

It has been difficult to prove the intermediacy of species such as 7 however, because of their very high electrophilic reactivity: there is either rapid reaction with available nucleophiles (*e.g.* nucleophilic solvent) or self-polymerisation. This reactivity has been related to the presence of low energy unoccupied molecular orbitals which give rise to acceptor orbitals localised at phosphorus[50]. However, indirect proof of the existence of metaphosphate species has been obtained from a number of trapping experiments, in which their reactivity towards nucleophiles is put to good use.

Monomeric methylmetaphosphate 7 generated in the gas phase by pyrolysis of methyl 2-butenyl-phostonate 8 was trapped in N-methylaniline as 9a, the N-methylanilinium salt of methyl N-methyl-N-phenylphosphoramidic acid (Equation 9)[51].

8

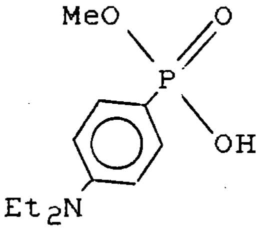
(9a)



9a

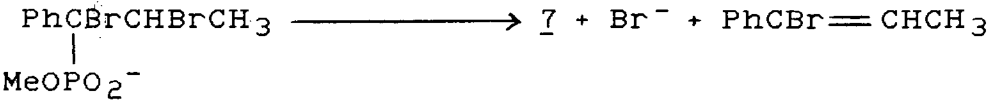
(9b)

Under similar conditions, N,N-diethylaniline trapped 7, but as methyl 4-(N,N-diethylamino)-phenylphosphonic acid 10a, the product of electrophilic substitution by 7 on the aromatic ring[52].



10a

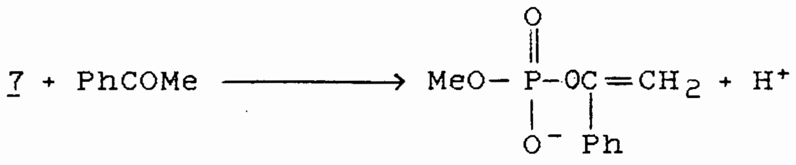
Similar results were obtained when 7 was generated in solution from 1-phenyl-1,2-dibromopropylphosphonates 11 (Equation 10)[53a].



$$\underset{\substack{|\\ \mathrm{MeOPO_2^-}}}{\mathrm{PhCBrCHBrCH_3}} \longrightarrow 7 + \mathrm{Br^-} + \mathrm{PhCBr{=}CHCH_3} \qquad (10)$$

11 10a

In addition, when the above reaction was carried out in the presence of acetophenone 7 was trapped as an enol phosphate 12 (Equation 11)[53b].



$$\underline{7} + \mathrm{PhCOMe} \longrightarrow \mathrm{MeO{-}}\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}\mathrm{{-}O}\underset{\underset{\displaystyle Ph}{|}}{C}\mathrm{{=}CH_2} + \mathrm{H^+} \qquad (11)$$

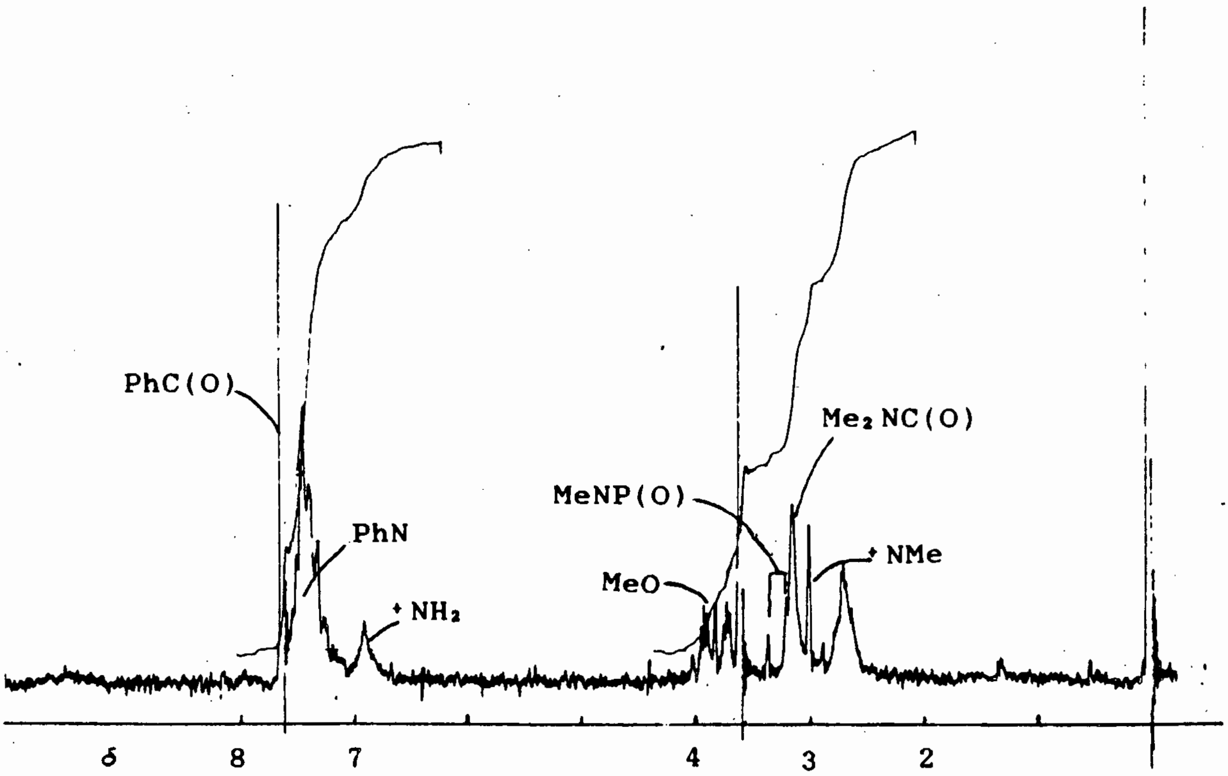
12

In view of the success of these experiments in indicating the intermediacy of metaphosphate moieties, it was decided to adopt the same approach to confirming the formation of 7 as an initial product of the phosphoryl to carbonyl centre nitrogen group transfer reaction.

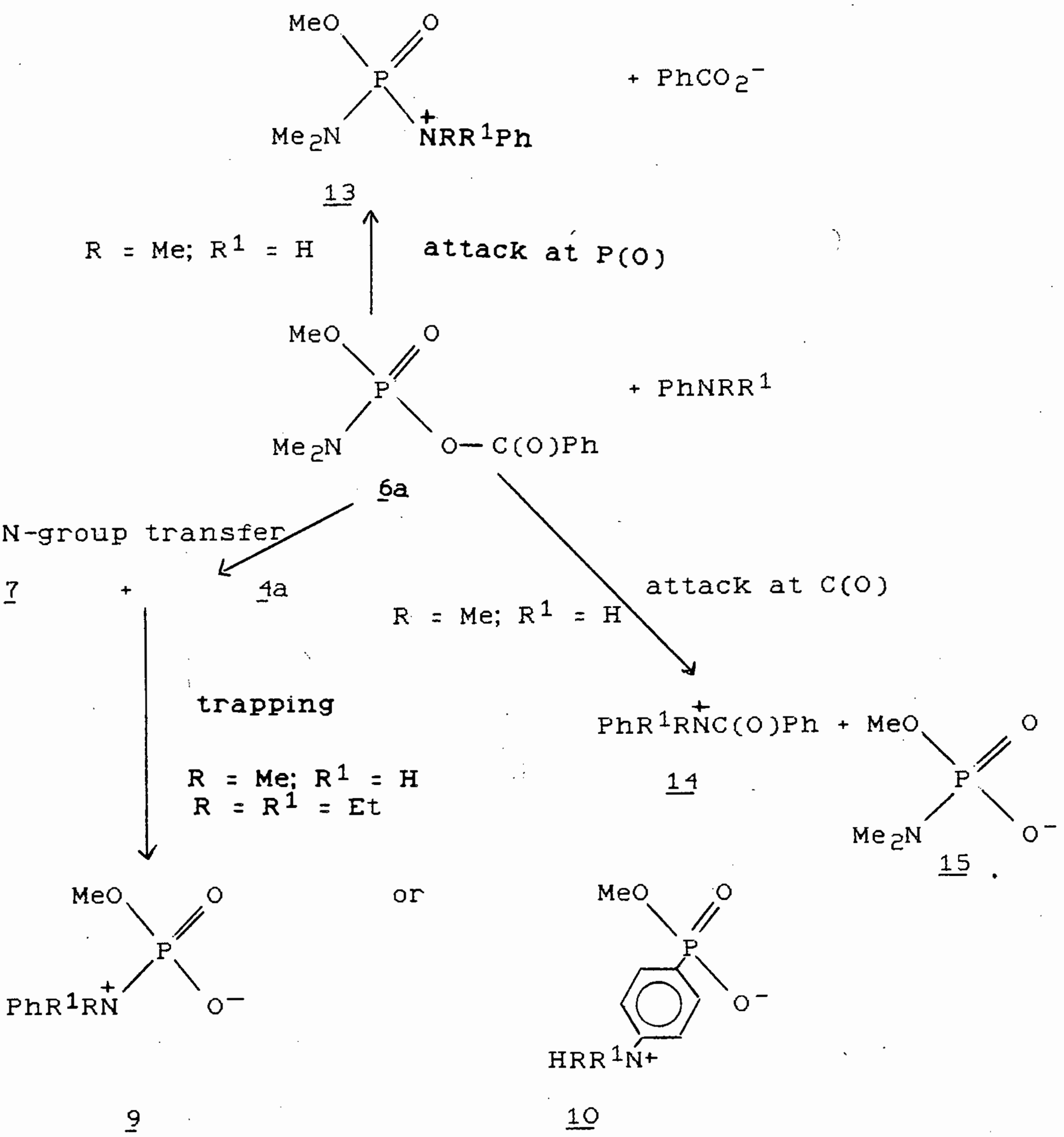
Initially, N,N-diethylaniline was the favoured trapping agent since, unlike N-methylaniline, no alternative reactions with 6a were possible, nucleophilic addition at phosphoryl or carbonyl centre requiring unfavourable quaternisation of nitrogen (Scheme 7).

A sample of 6a was dissolved in CD_3CN, and an equimolar amount of $PhNEt_2$ added; the solution was sealed in an nmr tube and heated at 65°C with periodic monitoring of the progress of reaction. After 64h the only change in the spectrum was the appearance of signals from 4a, with the accompanying reduction in those from 6a; there was no evidence for 10a. A similar result was obtained when $PhNMe_2$ was used. Heating of 6a in the presence of PhNHMe, however, gave positive trapping results. Figure 2 shows the ^1H nmr spectrum obtained after heating together, at 50°C for 60h, 6a and 2 equivalents of PhNHMe in CD_3CN. Formation of 9a is clearly indicated; in

Figure 2: ^{1}H nmr spectrum of 9a and 4a, formed by fragmentation of 6a in presence of PhNHMe. (60h; 50°C; $CDCl_3$; after evaporation of solvent and excess amine).



addition, 4a is also present, proving the simultaneous formation of monomeric methyl metaphosphate and carboxyamide by functional group transfer and fragmentation of mixed phosphoric-carboxylic anhydrides. There was no evidence at any stage during the reaction for species such as 13, 14 or 15, formed by chemical reaction between substrate and trapping agent.



Scheme 7

2.3.3 Solvent effects

Formation of carboxyamide 4 from mixed anhydrides 6 by intramolecular nitrogen group transfer followed by fragmentation requires formation of an activated complex or transition state which directly gives products. Three transition state structures can be envisaged (Figure 3). Figure 3a depicts an isopolar transition state, in which bond making and bond breaking processes occur in a synchronous manner, and the charge distribution differs very little from that in the reactant, whilst Figures 3b and c indicate dipolar cases, where there is considerable alteration in charge distribution compared to reactant[54]. Formation of the transition state requires energy, the free energy of activation, which according to Transition State Theory[55] can be described by the following equation.

$$k_R = \frac{RT}{Nh} e^{\frac{-\Delta G^{\ddagger}}{RT}} \qquad (12a)$$

where

k_R = reaction rate constant.

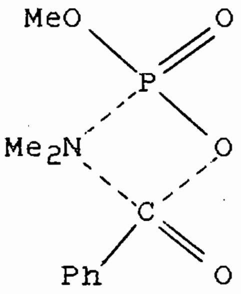
R = gas constant; T = absolute temperature; N = Avagadro's number; h = Planck's constant.

$\Delta G^{\ddagger}$ = free energy of activation.

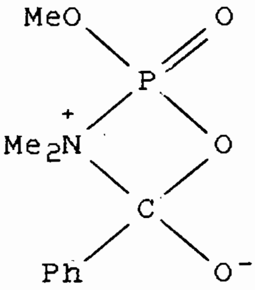
Thus, factors affecting the magnitude of $\Delta G^{\ddagger}$ will also alter the rate constant k_R: for reactions occuring in solution, more efficient solvation of the transition state than of reactants will lead to an overall reduction in free

Figure 3: Possible transition state structures for formation of 4a from 6a.

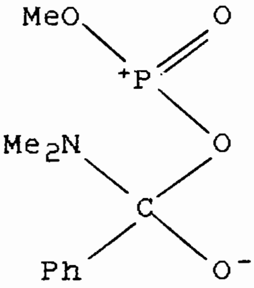
3a



3b



3c



energy of activation, and an increase in reaction rate, whilst the converse will be true if reactants are more efficiently solvated. Increases in both the magnitude and localisation of charge increase the extent of solvation by polar solvents. By observing variations in the rate of a reaction with changes in solvent polarity then, it is possible to deduce the nature of the transition state.

The rate of amino group transfer in 6a was measured as a function of concentration of 4a in a variety of solvents at different temperatures, and results are shown in Table 3. Due to the susceptibility of anhydride systems to undergo cleavage to the parent acids or acid derivatives in protic solvents, only dry, aprotic solvents could be considered for use in this study.

At any one temperature the rate varies by a maximum factor of 13 (k_1 (CCl_4): $k_1(CD_3CN)$; 72°C); for reaction at 45°C and 62°C, the rates vary by less than 5 and 9 times respectively, but the order of reactivity does not correlate with solvent dielectric constant or dipole moment values. Thus, there is a very small solvent effect on the rate of carboxyamide formation in 6a, implying little change in the charge distribution as the transition state is attained, and hence that the transition state is isopolar in nature. Because the substrate and transition state have different polarisabilities, interactions with solvent molecules will change during the course of the reaction, and it is these changes which lead to the observed small rate

Table 3: Solvent and temperature effects on rate of formation of 4a from 6a.

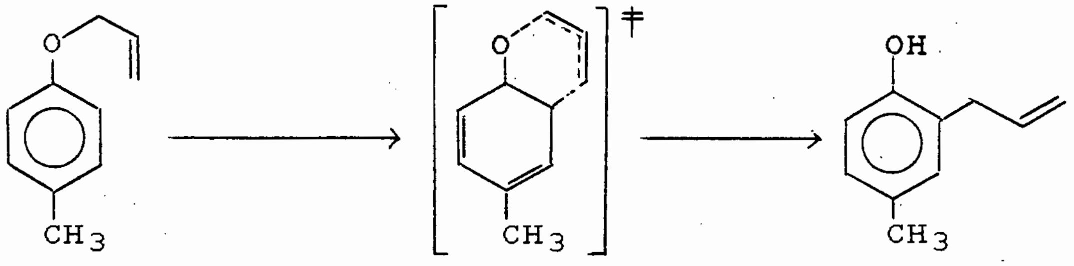
Solvent	CCl_4	$CDCl_3$	$(CD_3)_2CO$	CD_3CN
E^a	2.24	4.81	20.7^b	37.5
$\mu.10^{30c}$	0	3.84	9.54	11.48
Temperature (^oC)		$10^6k_1(s^{-1})$		
45	0.34	0.18	0.48	0.83
50				
58		0.72		
62	0.45	1.51	1.17	4.22
68			1.90	
71		4.56		
72	0.89		2.94	11.4

a dielectric constant measured at 20^oC

b dielectric constant measured at 25^oC

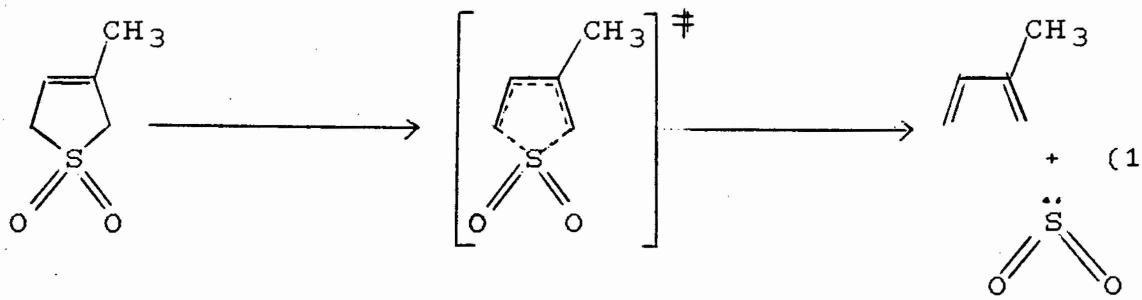
c dipole moment in Coulombmeter (Cm); measured at 20 or 30^oC.

variations. In support of this conclusion, the ortho-Claisen rearrangement of allyl p-tolyl ether, which involves concerted bond making and breaking (Equation 13), shows a rate enhancement of only 36 times when solvent changes from n-tetradecane to aqueous ethanol[56].



(13)

A reaction more closely related to that being investigated is the cheletropic fragmentation of thiophenoxides (Equation 14)[57].



(14)

Thermolysis of 3-methyl-2,5-dihydro-thiophen-1,1-dioxide involves concerted fission of two S-C σ bonds; the rate varies by a factor of as little as 1.8 when solvent is changed from n-decane to sulfolane.

In contrast, various addition reactions to alkenes, which involve dipolar transition states and ionic intermediates, have been shown to occur at least 100 times faster as solvent polarity is increased, even over a fairly small range: the addition of bromine to 1-pentene in water is 10^{10} times faster than in carbon tetrachloride, whilst alkene epoxidation by peroxybenzoic acid is 122 times faster in chloroform than when reaction occurs in diethylether[55].

Equation 12a can be shown in the form

$$k_R = \frac{RT}{Nh} e^{\frac{-\Delta H^{\ddagger}}{RT}} \, . \, e^{\frac{-\Delta S^{\ddagger}}{R}} \qquad (12b)$$

where

$\Delta H^{\ddagger}$ = enthalpy of activation

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

enabling interpretation of solvent effects in terms of these thermodynamic parameters. Although the Hughes-Ingold rules for solvent effects assume that the entropy contribution to a change in the free energy of activation of a reaction is small compared to the enthalpy term, this is not necessarily so; entropy changes can influence the free energy of activation, and thus the response of reaction to solvent variation[55].

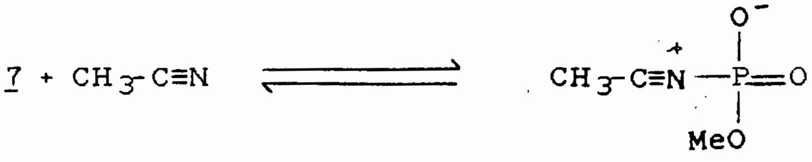
From the data in Table 3 it was possible to prepare Arrhenius plots and so calculate activation parameters for the nitrogen group transfer process. The results are shown in Table 4; a reliable plot could not be obtained for reaction in carbon tetrachloride.

Table 4: Activation parameters for formation of 4a.

Solvent	$CDCl_3$	$(CD_3)_2CO$	CD_3CN
r^a	0.995	0.985	0.979
$E_a{}^b$ (kcalmol^{-1})	27.9	14.4	19.7
$\Delta H^{\ddagger}$ (kcalmol^{-1})	27.3± 2.0	13.5± 2.0	20.7±0.7
$\Delta S^{\ddagger}$ (calK^{-1}mol^{-1}	-4.0±5.6	-42.6 ± 5.0	-21.4±4.8

a correlation coefficient for Arrhenius plot.
b from lnk vs 1/T plot.

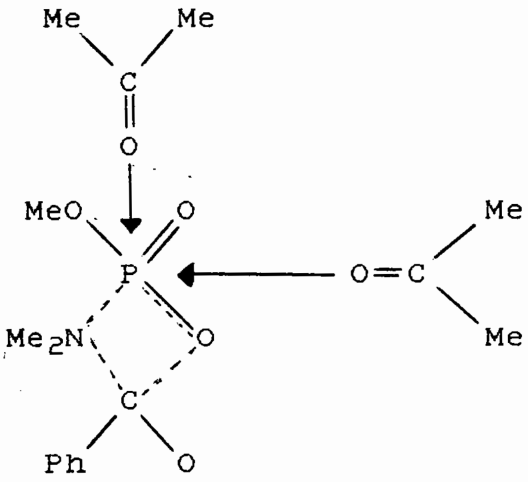
Although the $\Delta H^{\ddagger}$ values decrease by a factor of 2 over the range of solvents, implying some polarity in the transition state and variable efficiency of solvation, the direction of enthalpy change does not correlate with increasing solvent polarity. Since the observed rate changes are small, and therefore also the $\Delta G^{\ddagger}$ changes, the $\Delta H^{\ddagger}$ contribution to the free energy of activation cannot be dominant in this case: obvibusly the contribution of entropic energy is important. The entropy values decrease in the same order as the enthalpy terms. Since a decrease in entropy is unfavourable, implying greater ordering of the system, the favourable effect of decreasing enthalpy is effectively cancelled. We believe that this ordering of solvent in the transition state is related to nucleophilic solvation of incipient monomeric methylmetaphosphate. Because of its low energy, acceptor molecular orbitals, 7 is a strong Lewis acid, and is able to interact even with weak Lewis bases. Westheimer and Satterthwait have shown that the yield of products arising from aromatic electrophilic substitution by metaphosphate is diminished when reaction occurs in acetonitrile[58], and similar effects have been observed in studies on enol phosphate formation[59]. The reduction in reactivity of metaphosphate has been explained by proposing adduct formation with solvent:



$$\underline{7} + CH_3\text{-}C{\equiv}N \rightleftharpoons CH_3\text{-}C{\equiv}\overset{+}{N}\text{—}\underset{MeO}{\overset{O^-}{P}}{=}O$$

16

Such an adduct, between quinuclidine and monomeric metaphosphate anion, has been observed by ^{31}P nmr[60]. Formation of species such as 16 "freezes out" the solvent molecules, fixing them in a particular arrangement and so lowers the entropy of the system. Therefore, we attribute the observed unfavourable entropy changes in the transition state during formation of 4a in acetone to similar but even stronger Lewis acid-base interaction between the incipient 7 and the carbonyl oxygen of the solvent (17), exactly as is postulated in the mechanism for enol phosphate formation[59]. The analogous, but weaker, interaction with less basic acetonitrile would account for the smaller but still unfavourable change observed in this solvent.



17

In conclusion then, the rate data and activation parameters obtained favour formation of a transition state in which there is no significant charge development relative to substrate i.e. isopolar, and in which specific (related to acid-base interactions), rather than general, solvent effects operate.

2.3.4 Substituent effects

For reactions taking place in the side chain of an aromatic molecule it is often possible to obtain information about charge development in the transition state, and hence mechanistic information, by means of substituent effect studies and application of the Hammett equation (Equation 15)[61], which relates the energy changes in a reaction to the dissociation of benzoic acid and its derivatives, in what is termed a linear free energy relationship.

$$\log k/k_0 = \sigma\rho \qquad (15)$$

where

k = rate constant for side chain reaction of m- or p-substituted aromatic derivative

k_0 = rate constant for unsubstituted component

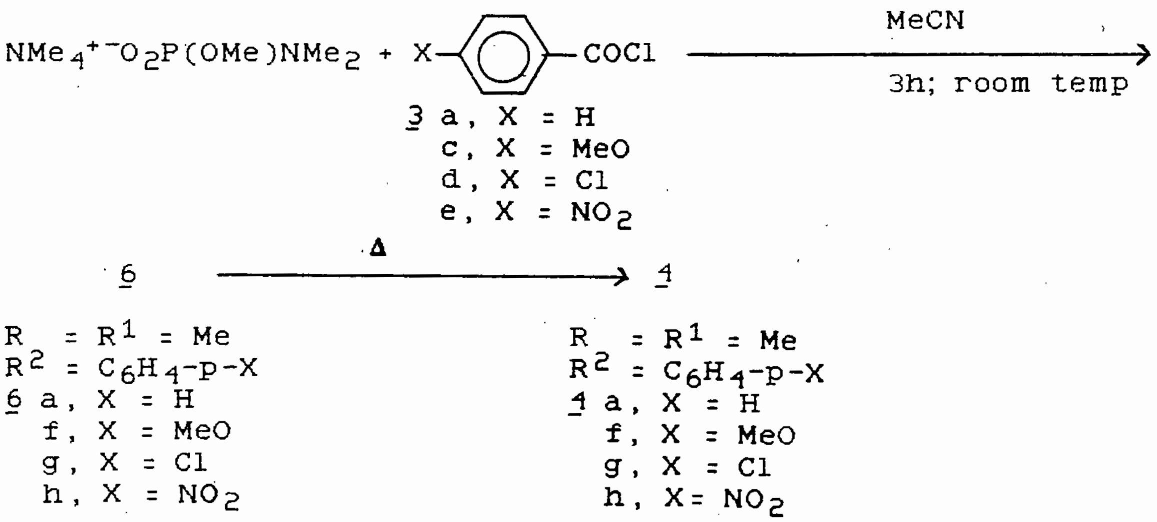
σ = substituent constant

ρ = reaction constant

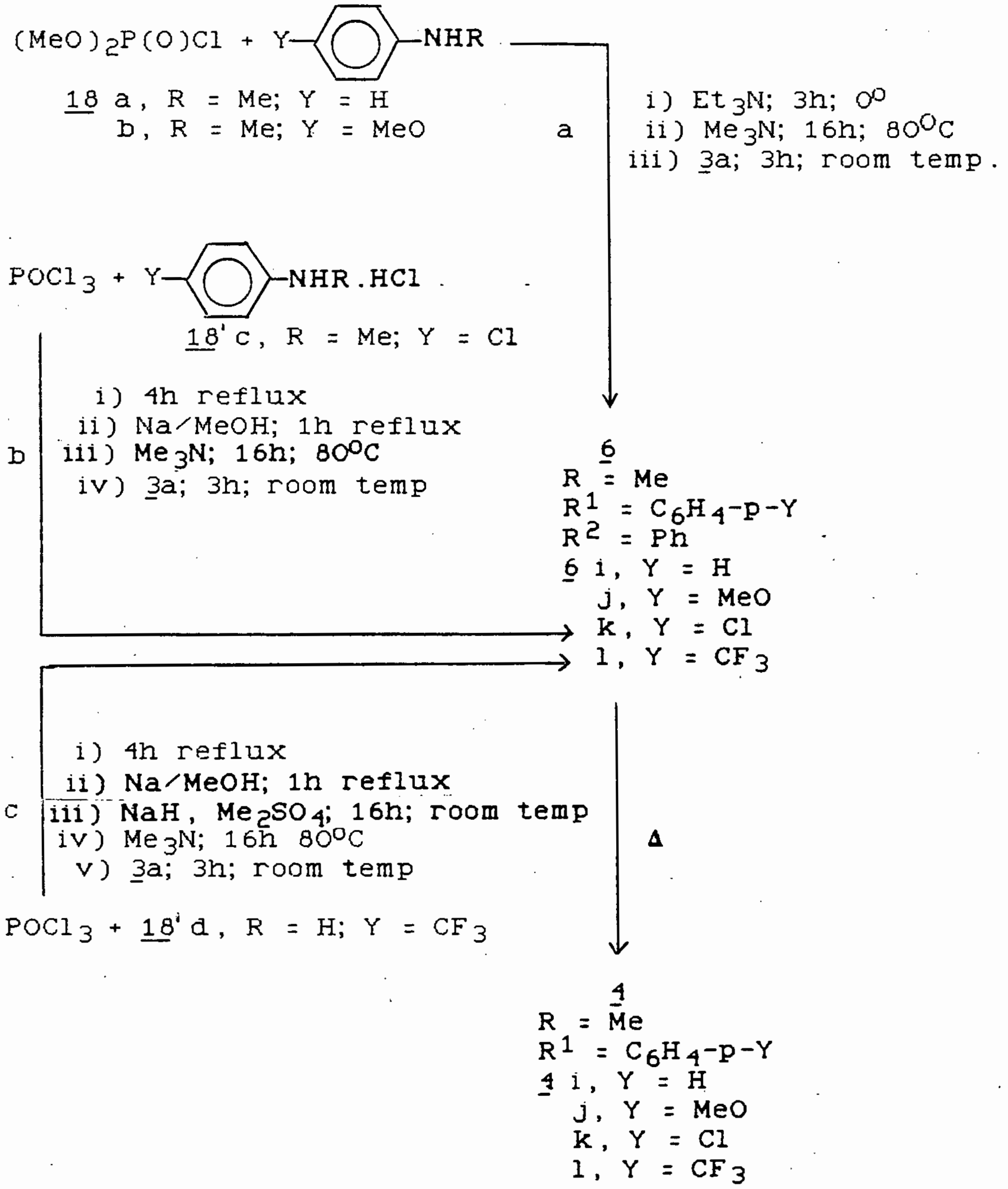
In the transition state, a change leading to localisation of charge at the side chain reaction centre can result in stabilisation or destabilisation of the system by inductive and resonance interactions with meta- and para-substituents on the aromatic ring, depending on the electronic nature of these groups, with resulting variations in the rate of reaction. If a correlation exists between reaction rate constant and substituent constant σ (a quantitative measure of the electronic effect of a substituent, derived from benzoic acid derivative dissociation constants), then the slope of the straight line obtained is the reaction constant ρ, which yields information about the magnitude of the charge change and whether it is positive or negative. Thus, ρ is a measure of the susceptibility of a reaction to substituent effects; for the dissociation of benzoic acids ρ is defined as 1.00. A positive ρ value indicates that electron-withdrawing substituents (i.e. with positive σ) accelerate the reaction.

Since the solvent effect study indicated nitrogen group transfer occurs with little or no charge development in the transition state, we decided to obtain further support for our conclusions. If a dipolar transition state were to be involved, then large rate changes can be expected for corresponding changes in the electronic nature of substituents.

Two series of mixed anhydride substrates, differing in substituents at either the carbonyl centre or at nitrogen were prepared as shown (6) (Schemes 8 and 9).



Scheme 8



Scheme 9

All mixed anhydrides isolated were oils, although the intermediate secondary phosphoramidochloridates and esters in the synthesis of 6l were solids: conversion to a tertiary amino system by N-methylation obviously removes hydrogen bonding possibilities and lowers the melting point of the compound. Method b (or c) proved to be a more general and suitable way of preparing dimethyl N-aryl phosphoramidates;

yields were acceptable (*ca*. 50 - 80%) in spite of the presence of electron-withdrawing substituents tending to deactivate nitrogen as a nucleophile, and there was no unreacted aniline in the crude product mixtures as when method a was used (20 - 30%). It proved impossible to form any dimethyl N-methyl-N-(p-nitrophenyl) phosphoramidate by method a, and the yield of the p-chlorophenyl analogue was increased from 30 to 50% when method b was used instead.

The rate of either N,N-dimethylamino- or N-methyl-N-arylamino-group transfer in substrates 6a, f-l to yield carboxyamides 4a, f-l was measured in $CDCl_3$ at 70°C using ^1H nmr spectroscopy (Table 5).

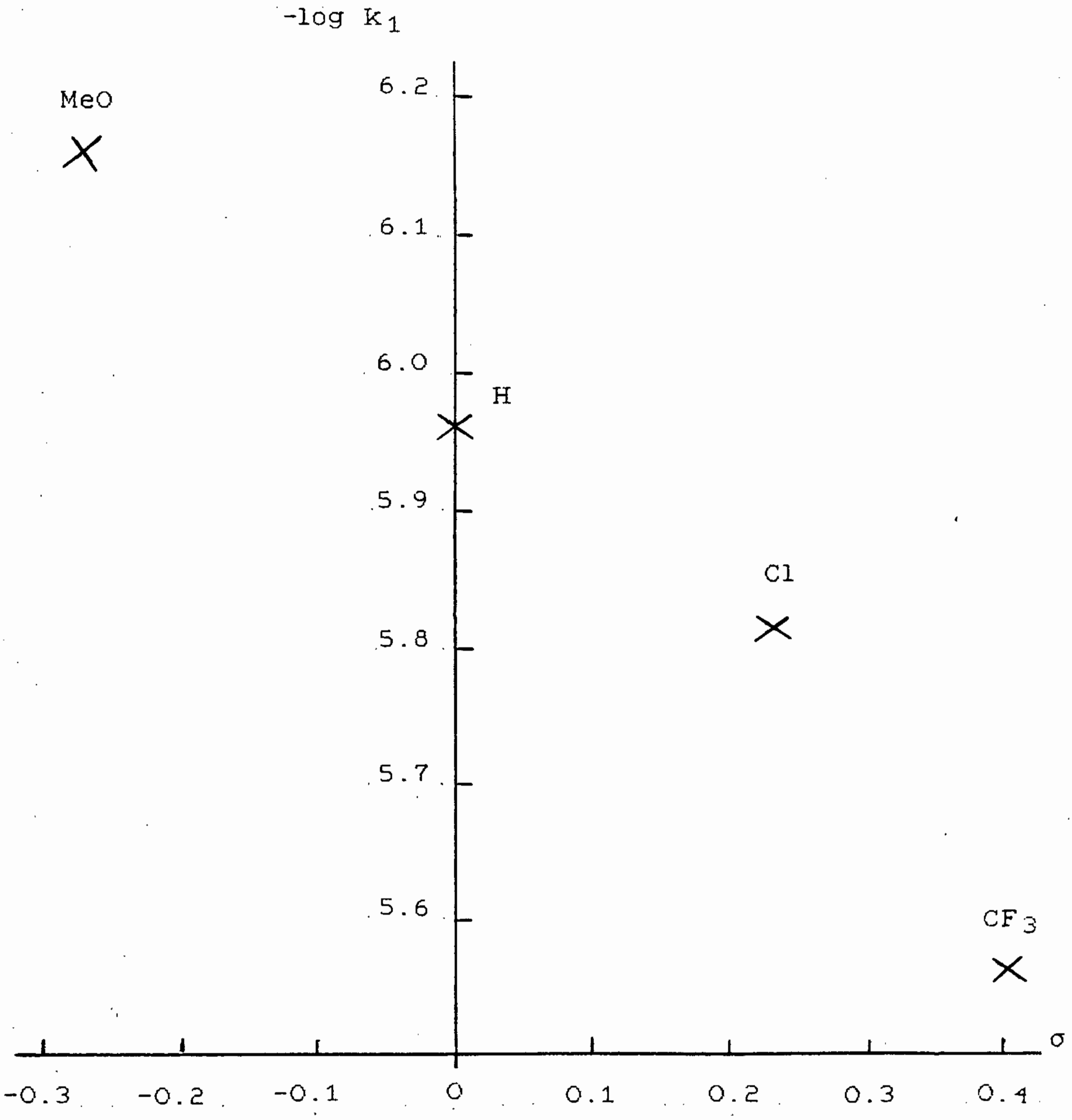
For variations in the nature of substituents at the carbonyl centre (6a, f-h) there is no correlation between the determined rate constants and substituent constant σ, or any other type of substituent constant e.g. σ_I. Over a range of 1.05 σ units the rate increases by 1.7 times. Substituent effects at the nitrogen group (series 6 i-l), however, result in a linear correlation with ρ value of +0.85 (r = 0.981; Figure 4), but again the overall effect on rate is weak, with 6l being just 4 times as reactive as 6j, and approximately half as reactive as 6a. The latter can be attributed in part to the effect of changing one substituent at nitrogen, from the weakly positively inductive methyl group to the more strongly negatively inductive aromatic nucleus, on the availablity of the nitrogen lone pair. Increased steric requirements may also contribute to the

Table 5: Rates of formation of 4a,f-l from 6a, f-l at 70°C in $CDCl_3$.

Substrate	X	Y	σ^a	$10^6 k_1 (s^{-1})$
6f	MeO		-0.27	4.1
6a	H		0	5.1
6g	Cl		0.23	2.2
6h	NO_2		0.78	2.4
6j		MeO	-0.27	0.69
6i		H	0	1.09
6k		Cl	0.23	1.53
6l		CF_3	0.40	2.74

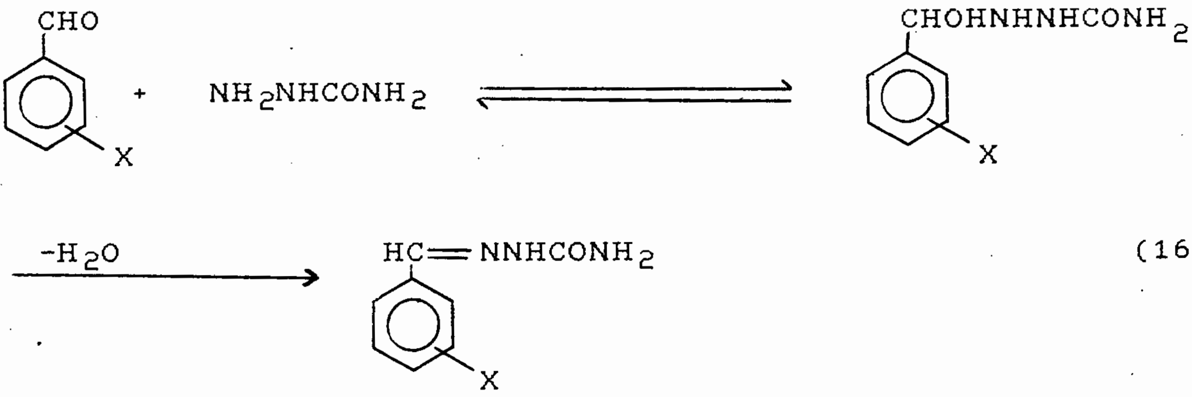
[a] from Ref.61.

Figure 4: Hammett plot for 6i-1.



reduction in reactivity of the N-aryl-substituted anhydrides.

Similar reactions in which there is attack of a nitrogen nucleophile at a carbonyl centre show better defined linear free energy correlations. For instance, in their work on aryl semicarbazone formation (Equation 16) Anderson and Jencks showed that the overall ρ for the reaction between semicarbazide and substituted benzaldehydes at pH 1.75 was 0.91[62]. At pH 8, when the rate of the second step is negligible, ρ was 1.81.



(16)

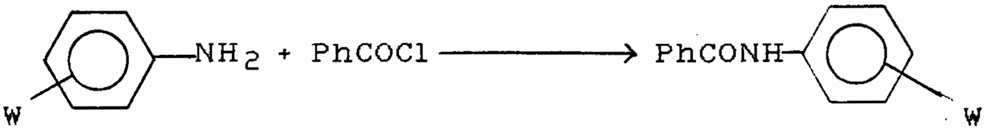
Similarly, data obtained from the N-acylation of secondary phosphoramidates (Equation 17) gave a Hammett plot with slope 1.8, which was interpreted as being "consistent with bimolecular nucleophilic attack at the carbonyl carbon atom"[63].

$$(EtO)_2P(O)NHMe + p\text{-}W\text{-}C_6H_4C(O)Cl \longrightarrow$$

$$(EtO)_2P(O)NMeC(O)C_6H_4\ p\ W \qquad (17)$$

W = H; Cl; Me

Anilide formation by reaction between substituted anilines and benzoyl chloride (Equation 18) was, on the other hand, characterised by a large negative ρ value of -3.21[64], electron-donating substituents increasing the nucleophilicity of nitrogen and so increasing rate.

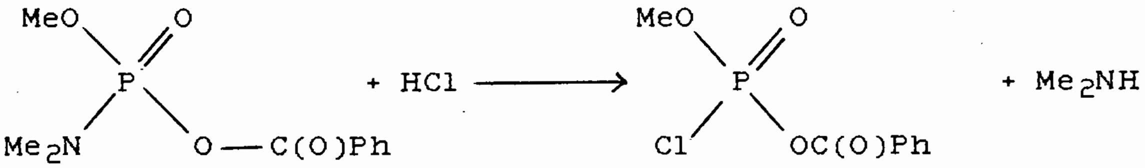


(18)

With regard to the mixed phosphoric-carboxylic anhydride systems 6, the results obtained indicate firstly, that there is little charge development in the transition state, in accordance with the concept of a concerted mechanism, since substituents at both centres show only small rate variations, and those at the carbonyl centre do not obey the Hammett relationship; secondly, it is departure of nitrogen from phosphorus rather than its approach at carbon that is important, as shown by the small, but positive ρ value. The electron-withdrawing effects of substituents in the N-substituted aromatic group destabilise the P-N bond, facilitating nitrogen group departure and increasing the rate of carboxyamide formation. This is a reversal of the trends normally observed for reactions giving similar products. Further evidence to support this proposal, obtained from molecular orbital calculations, will be presented (Chapter 3). The small variations in rate are attributed, at least partially, to a combination of conformational and specific solvent effects in the transition state, arising from the different substituent groups X and Y.

2.3.5 Lewis acid catalysts

Fairly early in our investigations we observed that in the presence of free benzoyl chloride (3a) the measured rate of formation of 4a from 6a increased, but to varying extents, depending on the amount of acid chloride present. This prompted us to investigate the role of 3a and other Lewis acids as catalysts in the amino group transfer process. 3a, iodine, antimony pentachloride and trifluoroacetic anhydride were all considered. $SbCl_5$ caused rapid P-N bond cleavage in 6a, probably because of initial reaction with traces of atmospheric moisture and HCl formation, and subsequent attack of acid at the P-N bond (Equation 19). Consequently very little carboxyamide transfer product was formed even when less than one equivalent of catalyst was used.



(19)

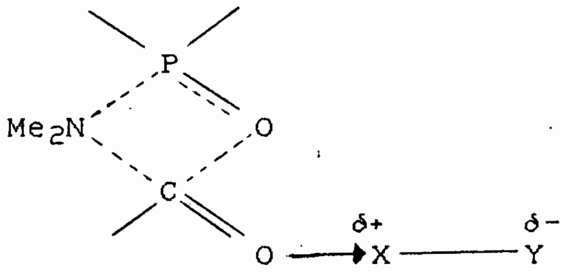
$(CF_3CO)_2O$ appeared to speed up the reaction, but there was evidence of alternative reactions taking place and use of this Lewis acid as a catalyst was also abandoned. The nature and course of these unexpected reactions will be the subject of later discussion (Chapter 6).

The results of our study using 3a and I_2 as catalysts in the fragmentation of 6a are given on Table 6. Both Lewis acids cause rate accelerations of up to 12 times over the

Table 6: Effect of Lewis acid catalysts on rate of 4a formation. (45°C).

Solvent	Catalyst	Concentration (M)	10^6k_1 (S^{-1})	k_{rel}
$CDCl_3$	-	-	0.144	1 1
[6a] =0.28M	3a	0.065	1.40	9.7
	3a	0.26	1.67	11.6
CCl_4	-	-	0.35	1
[6a] =0.28M	I_2	0.033	1.64	4.7
	I_2	0.118	2.49	7.1

concentration ranges considered. This catalysis is believed to arise from complexation between incipient basic carboxyamide in the transition state and added Lewis acid (19); this favours carboxyamide formation and so accelerates P-N bond cleavage.



XY = I-I; PhC(O)-Cl

19

N,N-dimethyl acetamide is known to complex to I_2 through carbonyl oxygen to form a 1:1 complex[65], and spectroscopic evidence has also been obtained for complex formation between I_2 and other N,N-dimethylcarboxyamides[66]. Formation of the complex between 4a and I_2 in CCl_4 at 25°C was accompanied by a free energy change of -0.8 $kcal\,mol^{-1}$ [67], and other workers have reported equilibrium constants of the order of $10^2 - 10^3$ for complexation between covalent halides and carboxyamides[68]. It thus seems likely that, in the absence of competing reactions, Lewis acids can catalyse carboxyamide formation from mixed anhydrides of the type 6.

2.3.6 Summary

The results of the kinetic investigation into the mechanism of phosphoryl to carbonyl migration of nitrogen functional groups in phosphoramidic acid/acid chloride systems (Scheme 3) reveal that

i) reaction occurs with formation of an intermediate mixed anhydride 6, which can be isolated;

ii) transfer of the nitrogen group occurs within 6 in a concerted, intramolecular process, *via* an isopolar, four-centre transition state (Figure 3a);

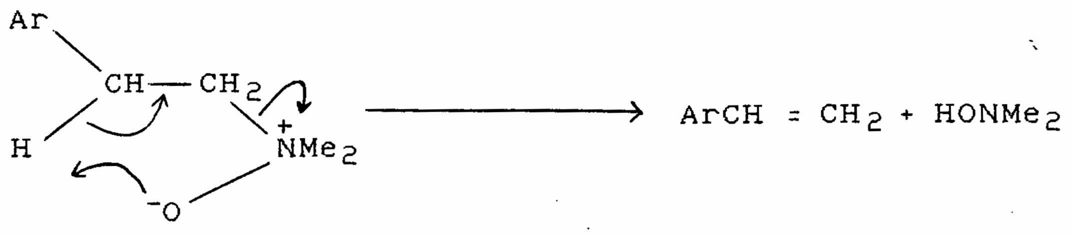
iii) 6 fragments into two products, carboxyamide 4 and monomeric methylmetaphosphate (Equation 20);

$$\begin{aligned}&\mathrm{MeO(RR^1N)PO_2{}^{-+}NMe_4} + \mathrm{R^2COCl} \longrightarrow \\ &6 \longrightarrow \text{transition state} \longrightarrow 4 + 7 \qquad (20)\end{aligned}$$

iv) since no carboxylic ester products were observed in the course of the study, the transfer reaction is specific to the transfer of amino groups;

v) there are specific interactions between incipient products in the transition state with solvents able to behave as Lewis bases, or with added Lewis acids.

The reaction thus resembles the pyrolytic elimination (E_i) reactions of acetates, xanthates (Tschugaev reaction) and amine oxides (Cope elimination), (Equation 21).[33,69]



(21)

These reactions all obey first order reaction kinetics, have negative entropies of activation and are often stereoselective, giving syn elimination products; the reactions are believed to proceed in a concerted fashion *via* an isopolar, cyclic transition state.

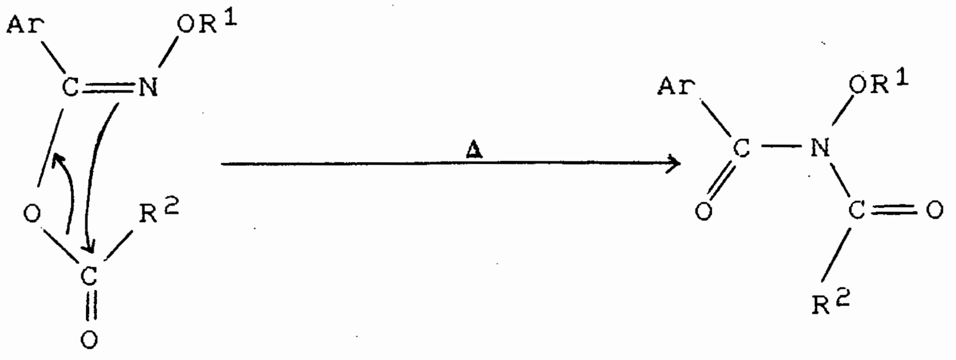
CHAPTER THREE

MNDO - SCF MOLECULAR ORBITAL CALCULATIONS

3. MODIFIED NEGLECT OF DIFFERENTIAL OVERLAP SELF-CONSISTENT FIELD MOLECULAR ORBITAL CALCULATIONS

3.1 Introduction

Molecular orbital theory makes use of complex mathematical formulations to simulate models of real chemical structures[70]. These models, in the form of energy matrices, are arrived at by consideration of the fundamental laws governing the formation of molecules from constituent atoms, enabling realistic simulation of chemical behaviour and examination in quantitative terms. The technique is a useful tool for providing evidence for or against chemical hypotheses. For instance, a detailed structure - reactivity study on the mechanism of the isomerisation of (E)-acyl O-alkylbenzohydroximic anhydrides 20 to N-acyl-N-benzoyl-O-alkylhydroxylamines 21 resulted in the proposal that the reaction took place by an intramolecular [1,3] acyl group migration with formation of a four-membered transition state[71].



20 21

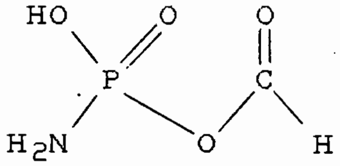
However, it is also possible that reaction occurs either with formation of a zwitterionic, four-centre intermediate, or by a concerted, sigmatropic rearrangement with conservation of orbital symmetry. A MNDO-SCF study in which reaction potential energy surfaces, and hence transition state structures, were calculated supported a concerted rearrangement via a four-centre intermediate, and also supported the observed solvent and substituent effects[72].

In a similar study, results from MNDO calculations on model phosphoric-carboxylic imide, $X_2P(O)NRC(O)R^1$ and isomeric imidate systems, $X_2P(O)OC(NR)R^1$, correlated well with structural and other experimental data, and could be used to explain the reluctance, under normal conditions, of such systems to undergo imide-imidate rearrangements[73].

In view of the successful use of molecular orbital calculations in the above and other[74,75] cases, it was decided to use this technique to obtain additional support for the mechanism already proposed (on the basis of experimental data) for the transfer of amino substituents from phosphoryl to carbonyl centre in mixed anhydrides, and to investigate the observed selectivity of the reaction[76].

3.2 Results and discussion

Calculations were carried out on the model system 22, considering both OH and NH_2 group transfer (Scheme 10), using standard MNDO procedures[77], and employing a s/p valence shell basis set only.



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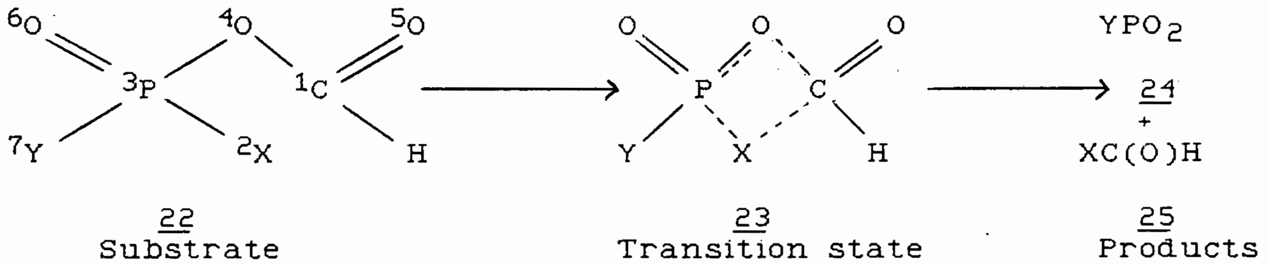
All 3N-6 geometrical variables were fully optimised. Using as a starting point an estimated transition state structure, putative transition states were located by minimisation of the sum of the square scalar gradients. The stationary points located were shown to be true transition states by calculating the force constant matrix and showing it to have only one negative root with eigenvectors corresponding to interconversion of reactant and product.



Y = OH or NH_2;

X = NH_2 or OH

Scheme 10

Since no other energy minima intermediate between reactant and product can be located, a concerted reaction is suggested, as predicted. Calculated energies and geometrical variables are shown in Tables 7 to 9 and Figure 5.

Table 7: Calculated MNDO bond lengths for 22, 23 and 25 (in Å)

	X = NH_2			X = OH	
Bond	22	23	25	23	25
1-2		1.554	1.473	1.479	1.355
2-3	1.667	1.851		1.796	
3-4	1.610	1.529	1.484	1.531	1.471
4-1	1.351	1.892		1.879	
5-1	1.272	1.218	1.214	1.219	1.227
6-3	1.497	1.481	1.483	1.480	1.470
7-3	1.667	1.594	1.596	1.646	1.604

Table 8: Changes in calculated bond lengths

a) substrate to transition state

	X = NH_2		X = OH	
Bond	Δ(Å)	%	Δ(Å)	%
1-4	+0.541	+40	+0.528	+39
2-3	+0.184	+11	+0.129	+ 8

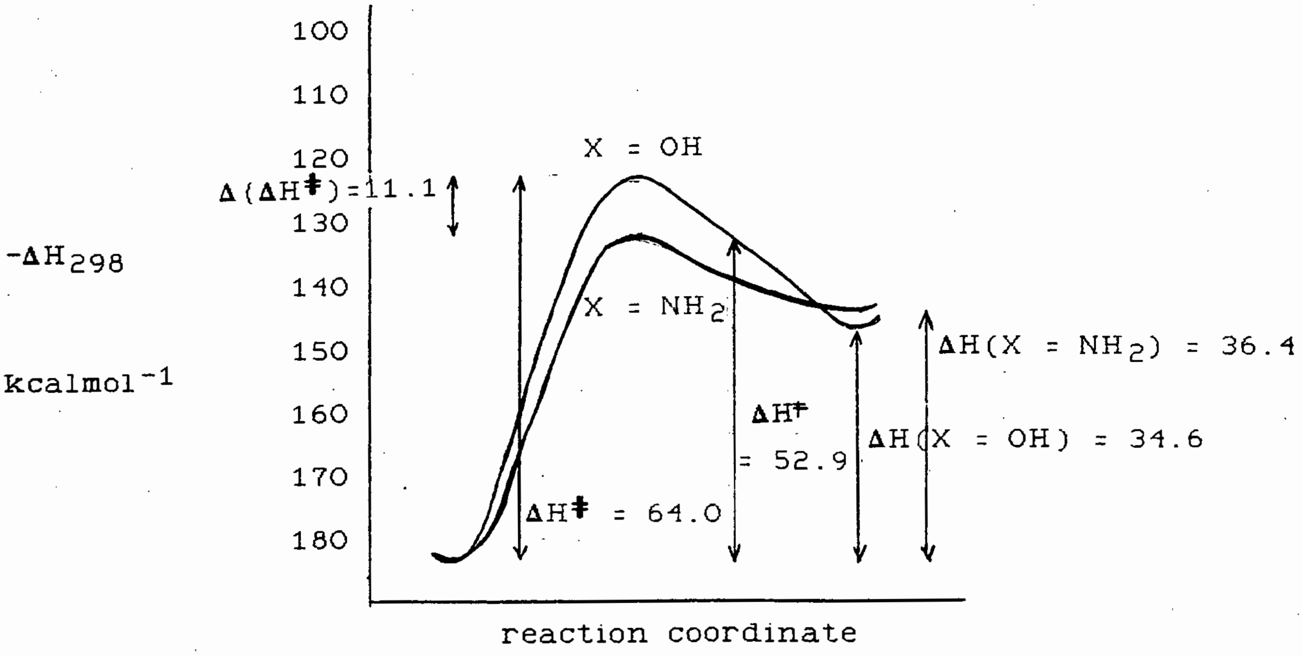
b) transition state to products

	X = NH_2		X = OH	
Bond	Δ(Å)	%	Δ(Å)	%
1-2	-0.081	-5	-0.124	-8

Table 9: Calculated MNDO energies and dipole moments (in $kcalmol^{-1}$ and D).

	X = NH_2			X = OH	
	22	23	25	23	25
ΔH_{298}	-183.1	-130.2	-146.7	-119.1	-148.5
D.M.	1.28	3.53	4.24	2.60	3.78

Figure 5: Schematic representation of calculated energies.



Although involving a 4-centre transition state, the calculations indicate the transfer reaction is not entirely synchronous: C-O (anhydride) bond cleavage is more advanced (40%) in 23 (X = NH_2) than P-N cleavage (11%), and similarly for the C-O and P-O bonds in 23 (X = OH) (Table 8). Since the transition states are not inherently symmetrical this asymmetry is not surprising; similar results have been found for gas phase dehydrochlorination of chloroalkanes[78], and have been calculated for Diels-Alder reactions involving unsymmetrical dienes or dienophiles[79]. There is a tendency for MNDO calculations to predict highly asynchronous or even stepwise diradical mechanisms[79], in which case the HOMO-LUMO energy gap in a spin-restricted Hartree-Fock MNDO calculation typically has a value of less than 8eV[80]. For the transition states considered here the corresponding orbital energy gap is greater than 10eV, implying that the prediction of a concerted reaction pathway is valid.

The enthalpy values obtained are of particular interest (Table 9; Figure 5). Formation of either carboxyamide or carboxylic ester is an endothermic process, requiring 36.4 or 34.6 $kcalmol^{-1}$ energy respectively. Furthermore, both processes have high activation barriers ($\Delta H^{\ddagger}$=52.9 and 64 $kcalmol^{-1}$), with transfer of the OH group requiring 11.1 $kcalmol^{-1}$ energy more than NH_2 group transfer.
Whilst errors can be expected in the absolute energy values, owing to the high formal oxidation state of phosphorus in this system[77], comparison of energies should show smaller

errors. In this vein, it should be pointed out that the calculated changes in dipole moments for transition state and product formation (Table 9) are large, and would seem to contradict the observed small solvent and substituent effects. However, since the calculations were carried out using only a s/p basis set of orbitals there will be a tendency for ionic contributions to the wavefunction to be emphasised. Inclusion of d-functions in the basis set would reduce this effect and the charge polarisation, as well as the calculated activation energies.

Since the total MNDO energies for the pairs of products obtained are very similar (Table 9; [-146.7 + $\Delta H(HOPO_2)$] vs [-148.5 + $\Delta H(H_2NPO_2)$]) it appears that differences in the relative stabilities of the products are not important in determining the selectivity of fragmentation:rather, the 11.1 kcalmol^{-1} difference in transition state energies is the deciding factor. This amount of energy is sufficient to prevent oxygen group transfer under the experimental conditions.

The origins of this energy difference were investigated by analysing relevant highest occupied molecular orbitals (Figures 6-8). For the low energy molecular orbitals corresponding to the forming σ bond between X and the carbonyl carbon there are significant differences for <u>23</u> (X = NH_2) and (X = OH) (Figures 6a,b). In the former case there is only one orbital where electron density is directed and localised along the C-N bond axis. For X = OH

Figure 6.

The molecular orbital (and its energy) corresponding to the formation of the σ bond between X and C; a, X = NH_2; b, X = OH.

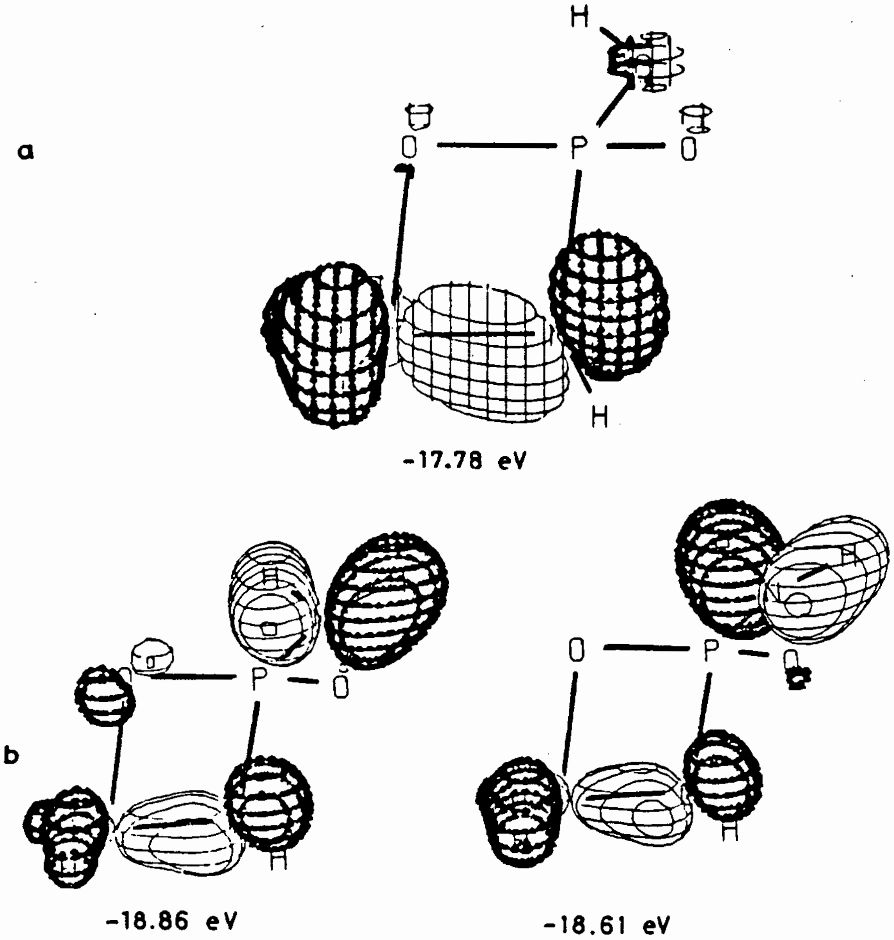


Figure 7.

The first molecular orbital with electron density in the plane of the POCX ring; a, X = NH_2; b, X = OH.

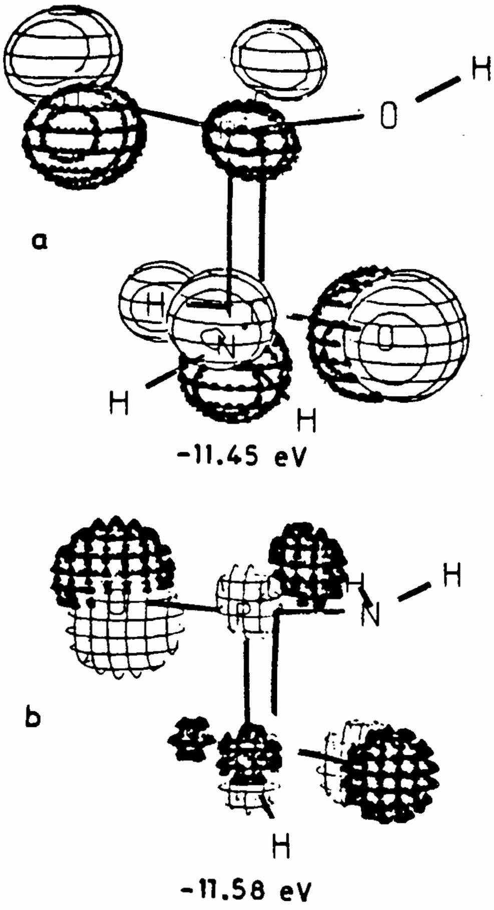
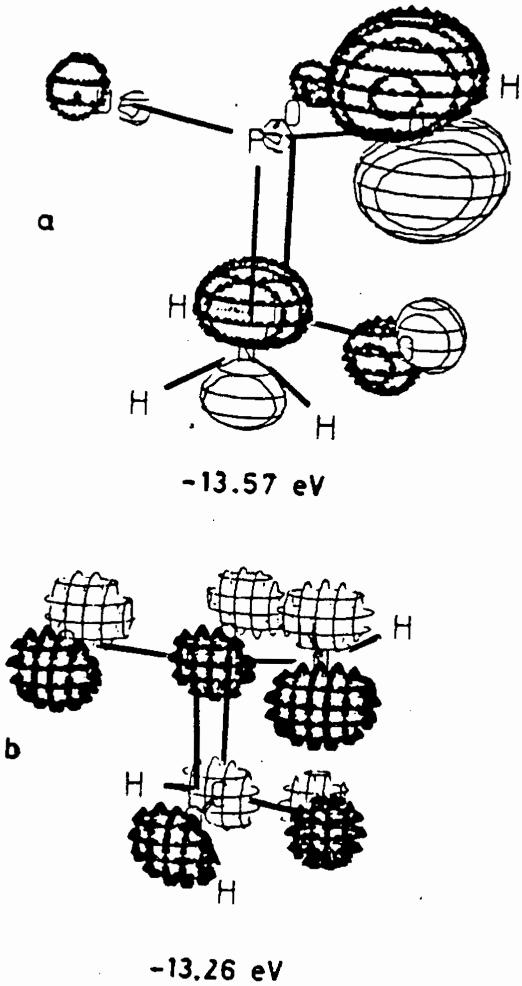


Figure 8.

Second molecular orbital with electron density in the plane of the POCX ring; a, X = NH_2; b, X = OH.



two orbitals can be located with some electron density along the C-O bond: both have less electron density in the region than in the nitrogen group transfer situation. These orbitals correspond to symmetric and antisymmetric combinations of a C-O σ bond with N-H σ bonds of the ring substituent, and tend to make the X = OH transition state less favourable, as well as susceptible to substituent effects at nitrogen.

When the HOMO-1 of the transition states, comprising of combinations of the exocyclic oxygen or nitrogen lone pairs, are considered, differences are again observed. Figure 7 shows the first molecular orbital for each case which displays significant electron density in the plane of the POCX ring. In both transition states there is density on the transferring oxygen or nitrogen group, as well as on anhydride, phosphoryl and carbonyl oxygens and formyl hydrogen. The component on nucleophilic nitrogen is greater (Figure 7a) than on nucleophilic oxygen (Figure 7b), implying firstly that nitrogen acts as a better nucleophile than oxygen in the transfer process, and also that substituents other than hydrogen at carbonyl carbon would stabilise the transition state for nitrogen group transfer. Such stabilisation effects would be much smaller in the oxygen group transfer transition state, where there is also a destabilising 1,3-interaction between orbitals on the two endocyclic oxygen atoms (Figure 7b).

A second molecular orbital with electron density in the ring plane can be located (Figure 8). Where X =NH_2 (Figure 8a), electron density is directed along the axis of the cleaving P-N bond, and is orientated in such a fashion that antiperiplanar interaction with the exocyclic hydroxy group lone pair is possible. Such an interaction constitutes the stereoelectronic effect[81], which has been shown by Kirby to lead to bond lengthening and reactivity changes in ground-state acetals[82]. In their work on stereoelectronic effects in phosphate diester reactions[83], Gorenstein *et al* showed that during hydroxide-catalysed hydrolysis of dimethyl phosphate the transition state leading to product formation was *ca* 11 kcalmol^{-1} lower in energy when the P-L (L = leaving group) bond was orientated in an antiperiplanar fashion to one of the lone pair orbitals on some heteroatom substituent X at phosphorus. It seems likely that in the mixed anhydride system a similar interaction between hydroxy group lone pairs and the cleaving P-N bond enhances nitrogen group transfer and so contributes to the specificity of the reaction. A corresponding stereoelectronic effect is not possible when the migrating atom is oxygen (Figure 8b) since the electron density on nucleophilic oxygen is not directed along the P-O bond, resembling instead a lone pair orbital: there is a destabilising interaction between this orbital and the NH_2 group lone pair which will raise the energy of the transition state.

Quantitative information about the model transition states, rather than the qualitative results presented thus far, were obtained by transforming the SCF molecular orbitals into localised orbitals[84]. This analysis assigns a bond number value of 1.0 to a localised lone pair, and the value 2.0 to a two centre orbital such as in H_2O. The values obtained for the system being investigated are summarised in Figure 9. For 23 (X = NH_2) (Figure 9a) analysis of the transition state reveals one orbital localised along the forming C-N bond and another along the cleaving P-N bond, with bond numbers of 1.857 and 1.444 respectively. The analogous bonds in the 23 (X = OH) case give values of 1.785 and 1.318 (Figure 9b). The implication is that there is a greater extent of new bond formation in the transition state where nitrogen is transferring. Since the C-N bond has characteristics of a two-centre orbital rather than a lone pair, the analysis supports late transition state formation. This finding can be related to the bond length data already presented (Table 8) which shows that for X = NH_2 the C-N bond distance changes by only 5% as reaction proceeds from the transition state to products: C-N bond formation is obviously almost complete in the transition state.

3.3 Conclusion

The results obtained from the molecular orbital calculations on model system 22 support the proposal that N-group transfer in mixed phosphoric-carboxylic anhydrides is specific and takes place intramolecularly in a concerted fashion, with

Figure 9. Localised orbital bond numbers in 23.

formation of a four-centre transition state. The analagous transfer of oxygen groups is unfavourable by virtue of the transition state having higher activation energy requirements, there being no stabilising stereoelectronic effects, and the involvement of other destabilising orbital interactions. Finally, the indication that stereoelectronic effects have an important part in the nitrogen group transfer process, and the localised orbital analysis both support the conclusion arrived at earlier, on the basis of substituent effects, that departure of nitrogen from phosphorus in the transition state is important.

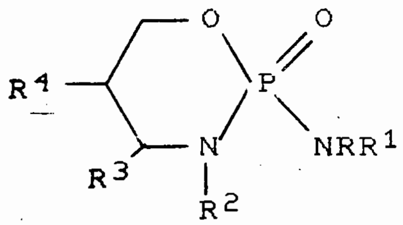
CHAPTER FOUR

EFFECTS OF CONFORMATION ON NITROGEN GROUP TRANSFER

4. EFFECTS OF CONFORMATION ON NITROGEN GROUP TRANSFER[85]

4.1 Introduction

Cyclic phosphorodiamidates related to cyclophosphamide (26a; 26b-e) are widely used anticancer agents, and have been studied in some detail with respect to their structure and absolute configuration[86-91], in order to determine which enantiomers have greatest activity, and their mode of action.



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a, $R = R^1 = CH_2CH_2Cl$; $R^2 = R^3 = R^4 = H$; cyclophosphamide

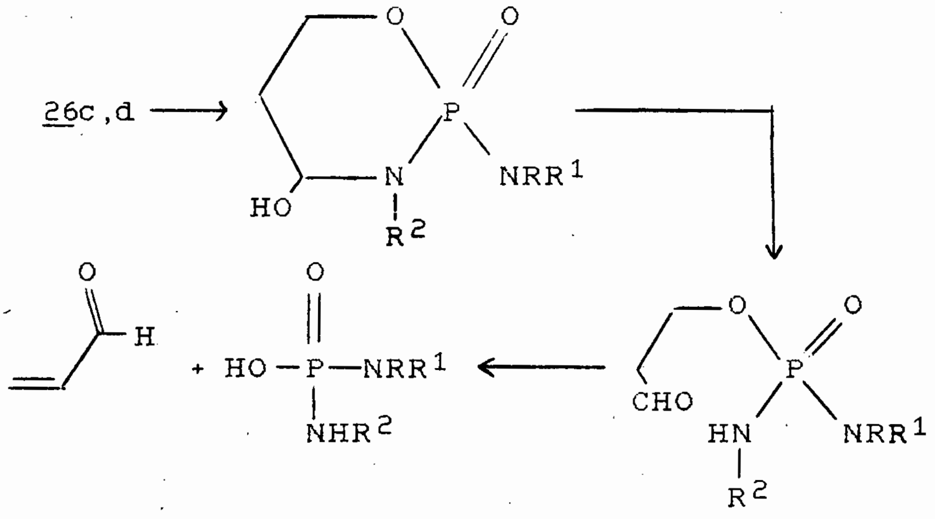
b, $R = R^2 = CH_2CH_2Cl$; $R^1 = R^3 = R^4 = H$; isophosphamide

c, $R = R^1 = CH_2CH_2Cl$; $R^2 = R^4 = H$; $R^3 = O_2H$;
4-hydroperoxycyclophosphamide

d, $R = R^1 = CH_2CH_2Cl$; $R^2 = R^4 = H$; $R^3 = O$
4-ketocyclophosphamide

e, $R = R^1 = CH_2CH_2Cl$; $R^2 = R^3 = H$; $R^4 = F$;
5-fluorocyclophosphamide

26c and d are believed to be metabolic products of 26a, which fragment further yielding acrolein (27) and phosphoramidate mustard (28), the latter being a DNA cross-linking agent responsible for the cytostatic activity of these compounds (Scheme 11).



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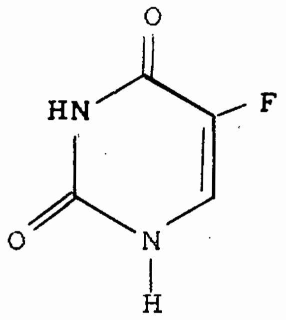
Scheme 11

The reactions of Scheme 11 have been utilised in the synthesis of a derivative of another chemotherapeutic agent, 5-fluorouracil (29).



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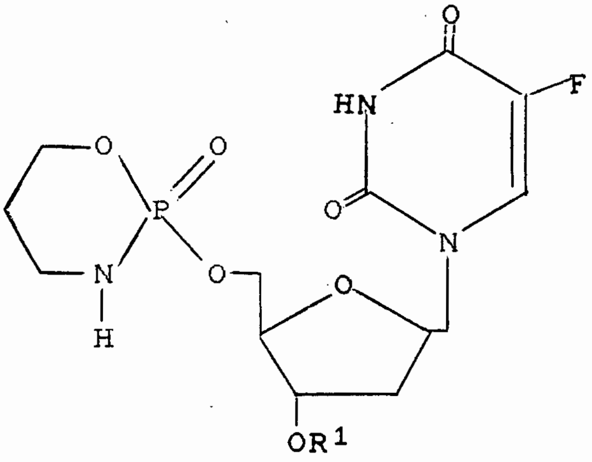
In order to increase the uptake of the drug by cells, and reduce its toxicity towards healthy tissue, the 2'-deoxyoxazaphosphacyclohexyluridine 30 was synthesised; this readily penetrates cell membranes and is enzymatically degraded (via Scheme 11) to 31, the active compound[92].



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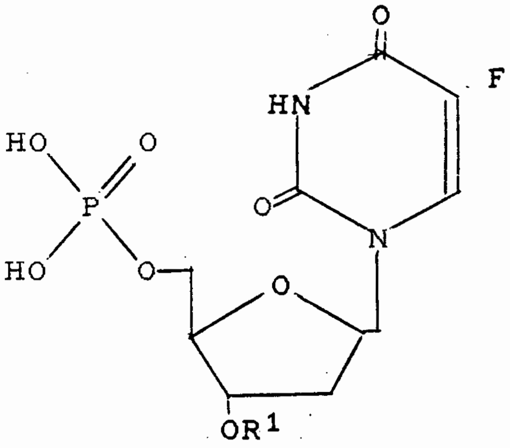

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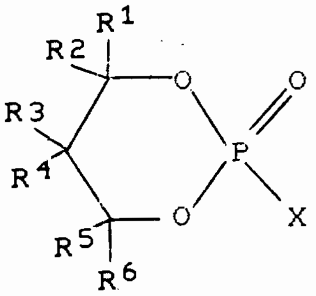
The medical importance of cyclophosphamide and other cyclic phosphates has thus stimulated research in this field. The stereochemistry of reaction of nucleophiles at phosphorus in five and six membered cyclic phosphates has been investigated in detail and recently reviewed[93], and a number of studies on the conformational preferences of cyclic systems have also been carried out[94-98]. In addition, the basicity of the phosphoryl group in dioxophosphorinanes (32) has been investigated by infrared spectroscopy[99],



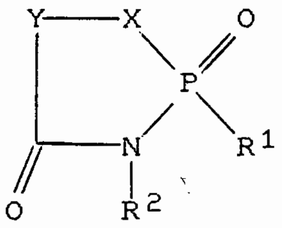
32

X = Cl; OPh; OMe; OEt; NMe_2

R^1 = H; Me; i-Pr

R^2,R^3,R^4,R^5,R^6 = H; Me; Ph.

and the comparative reactivity of oxazaphospholanes (33) towards alcohols and amines studied[100].



33

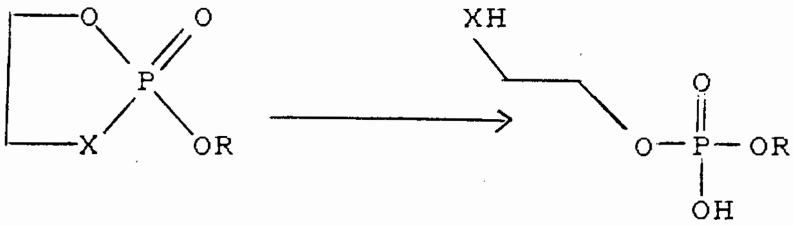
R^1 = aryl; alkoxy; aryloxy

R^2 = aryl; alkyl

X = NH; NMe; CH_2; NR; O

Y = CH_2; C(O); CMe_2

Oxazaphospholanes and dioxophospholanes 34 have been used as intermediates in phospholipid synthesis (Equation 22)[101],



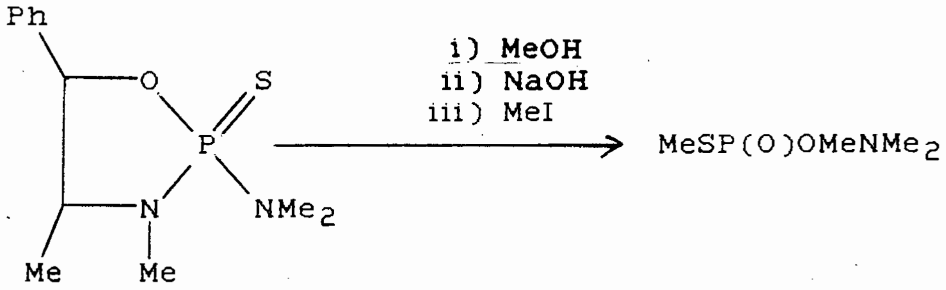
(22)

34

X = NMe; O

R = diacylglyceryl group

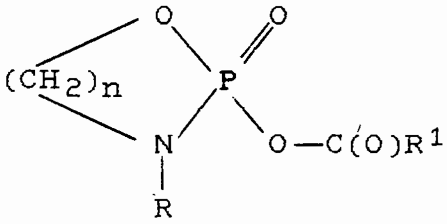
and oxazaphospholidine thiones (35) have been used in the synthesis of chiral O,S-dialkyl phosphoramidothioates (36) which are insecticides (Equation 23)[102].



(23)

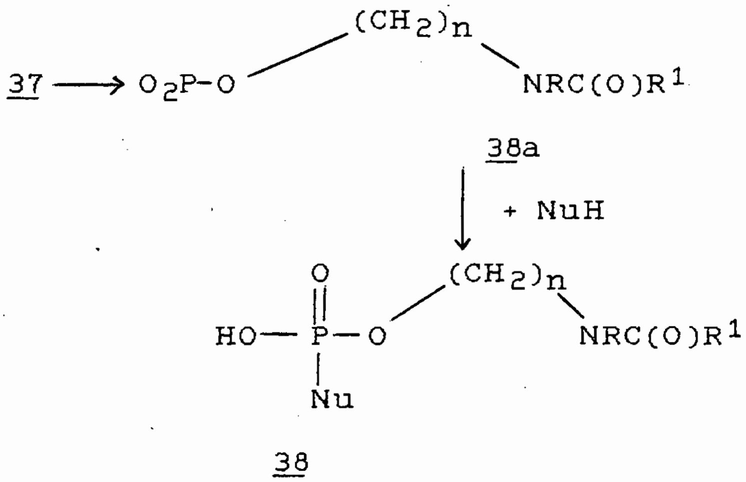
35 36

With respect to the elucidation of the mechanism of nitrogen group transfer in mixed phosphoric-carboxylic anhydrides: since there was evidence for formation of a four-centre, cyclic transition state, imposing conformational restraints on the system and possibly making transition state formation difficult could be expected to result in decreased reaction rates. Thus, by incorporating the amide and ester functions into a relatively inflexible ring system we hoped to obtain additional information about the mechanism. Also, functional group transfer in a cyclic system such as 37 would not result in fragmentation of the molecule, as the metaphosphate moeity would remain attached to the carboxyamide portion through a P-O bond to the alcoholic nitrogen substituent (38a).



37

Consequently, additional evidence for the simultaneous formation of both the expected nitrogen group transfer products would be obtained by successful reaction of the metaphosphate portion with a suitable nucleophile, since the resulting compound 38 would be a derivative of the rearranged starting material (38a; Equation 24).



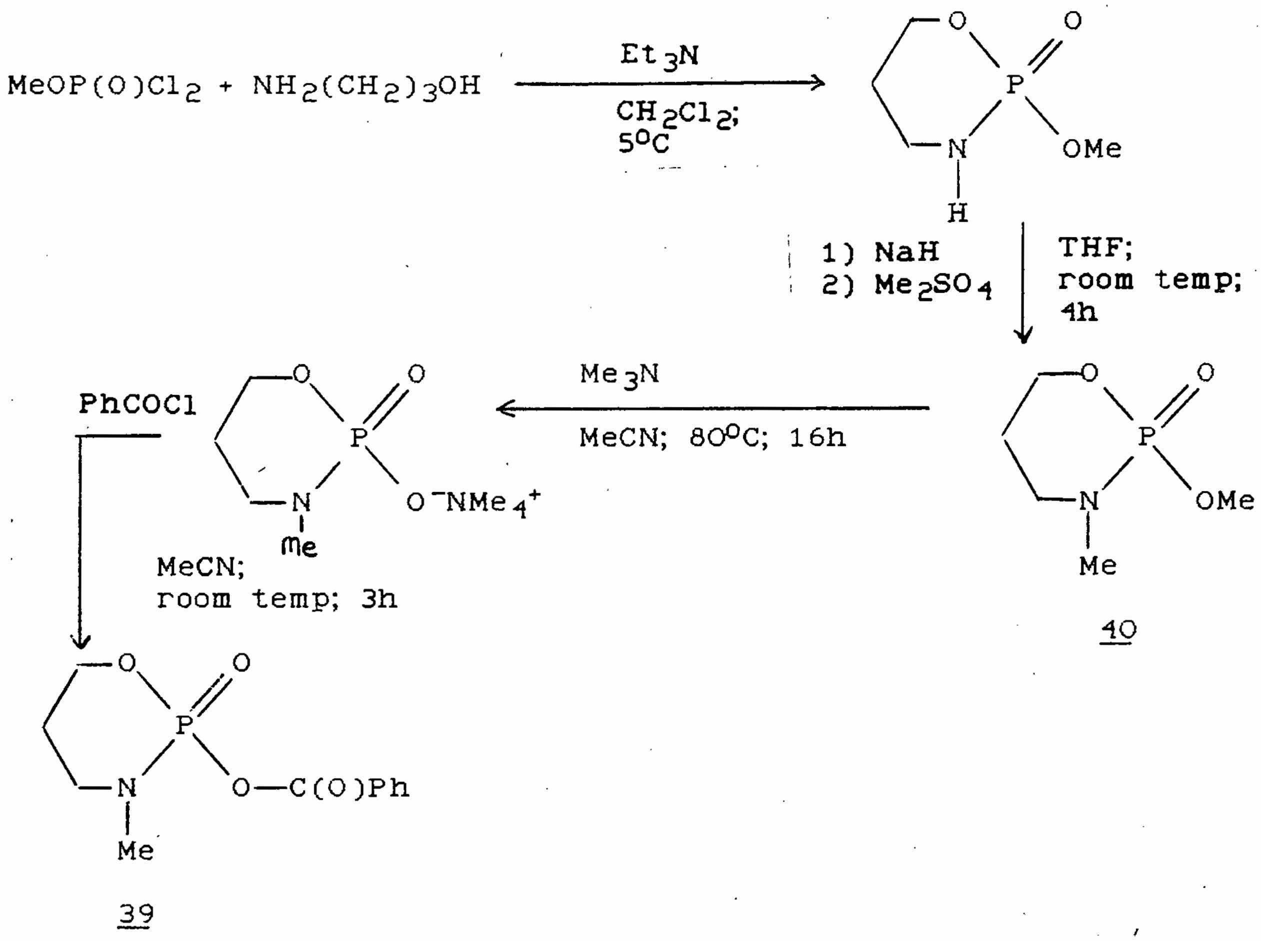
(24)

With these aspects in mind, it was decided to synthesise a cyclic mixed phosphoramidic carboxylic anhydride, and investigate its reactivity with respect to the nitrogen transfer process.

4.2 Structure and Reactivity of N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane.

4.2.1 Synthesis and Kinetic Study.

The synthesis of N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane, 39 is outlined in Scheme 12.

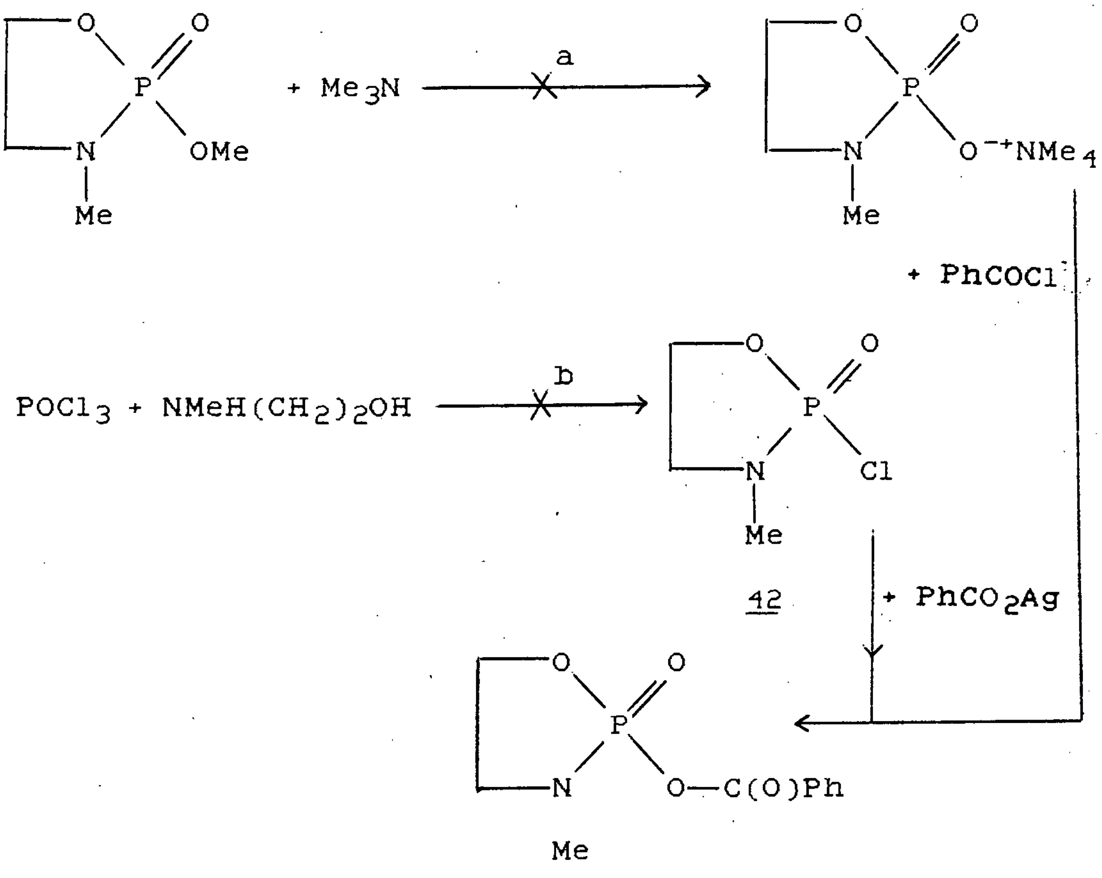


Scheme 12.

Unlike most of the other anhydride substrates previously prepared which were oils (except for $MeO(NMe_2)P(O)OC(O)C_6H_4$-p-X, X = NO_2; Cl), 39 was a waxy solid.

The use of methyl iodide rather than dimethyl sulphate in the synthesis of the tertiary amide 40 was attempted, but gave very poor yields, probably because of competing demethylation of both substrate and product by iodide ion.

The preparation of the five-membered analogue 41 proved unsuccessful (Scheme 13):



42

41

Scheme 13

Reaction a resulted in ring-opening rather than demethylation since both the α-carbon atoms of the two ester functions (-OCH$_3$; -OCH$_2$-) are equally susceptible to nucleophilic attack, while b[103] yielded a mixture of 42 and $Et_3NH^+Cl^-$: attempts to purify 42 resulted in its decomposition.

Preliminary experiments in which 39 was heated in $CDCl_3$ solution indicated that P-N bond cleavage and C-N bond formation was occurring: a new signal at *ca.* δ 3.0 in the ^1H nmr spectrum was observed, corresponding to the N-methyl and N-methylene protons of 38a (n = 3) (Figure 10). Using this signal as a probe, the rate of transfer was measured in $CDCl_3$ at 70°C for two solutions of 39 of known concentrations. The reaction obeyed first order kinetics (data points were scattered when incorporated into the second order rate law), and gave an averaged rate constant $k_1 = 8.63 \times 10^{-8} s^{-1}$ (Table 10), 53 times smaller than the rate constant for transfer in the acyclic analogue 6a. Attempts to trap the intermediate 38a by reaction with acetophenone, and so prove simultaneous formation of metaphosphates and carboxyamides by intramolecular transfer, were unsuccessful; other trapping agents were not used. Further investigations were directed towards determining the structural factors responsible for the lower reactivity of 39 with respect to the transfer-fragmentation reaction.

4.2.2. Structure determination and molecular mechanics study.

The fact that 39 was solid offered the opportunity of gaining an insight into the transition state requirements for nitrogen group transfer: Burgi and Dunitz claim that

Figure 10: 100MHz ^{1}H nmr spectrum of 39 after heating ($CDCl_3$; 70°C; 159h).

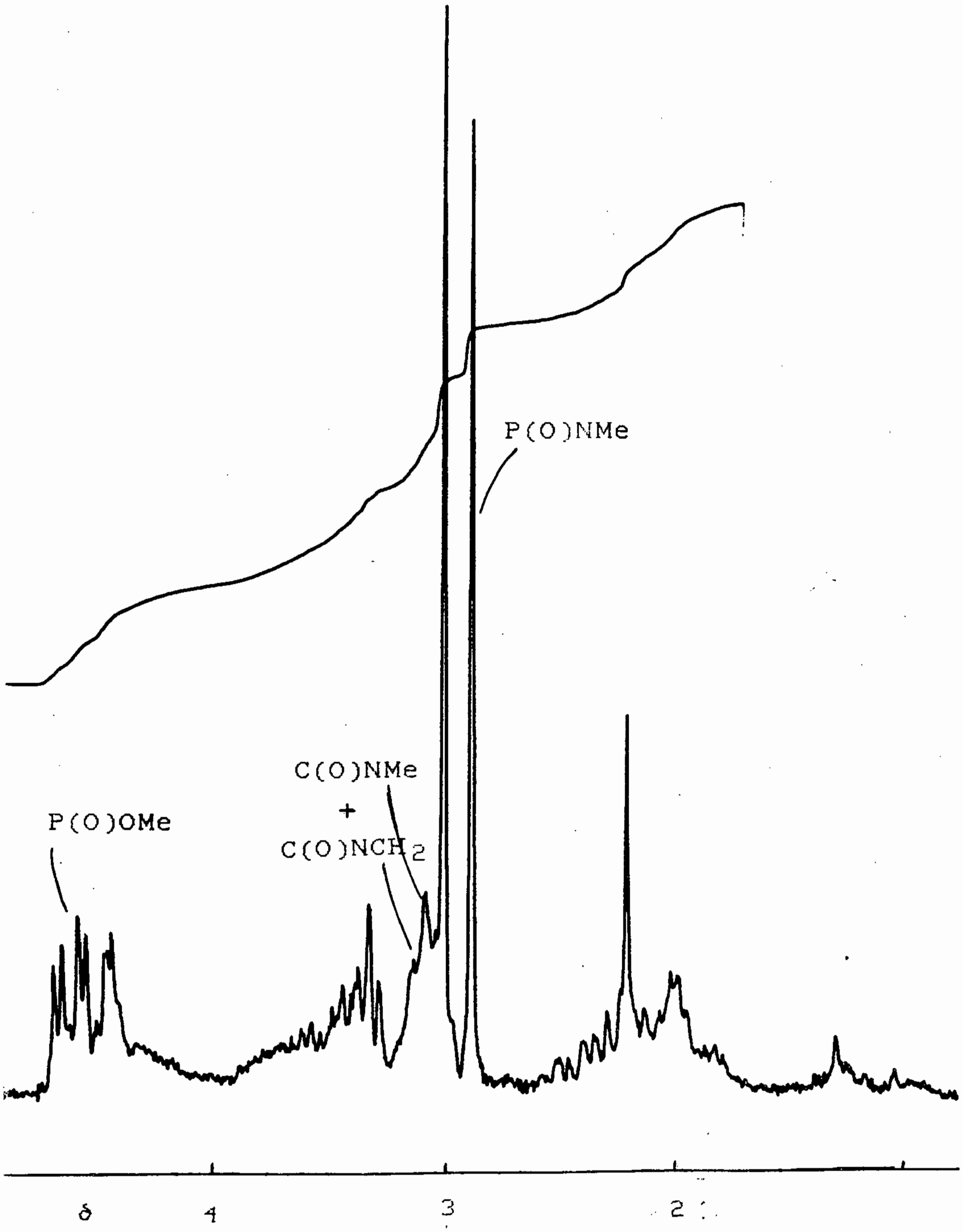


Table 10: Rate data for nitrogen group transfer in <u>39</u> ($CDCl_3$; 70^{o}C).

Concentration of <u>39</u> (M)	0.258	0.272
10^8k_1 (s^{-1})	7.61	9.64
r	0.8906	0.9706

regularities observed in the crystal structures of a series of systems containing both nucleophilic and electrophilic centres can be used to map energy pathways for reaction between the two centres, each structure representing a situation where reaction has been frozen, after proceeding to a certain extent, because of constraints imposed by the crystal environment[104]. In the same way, it was felt that the solid state structure of 39 might resemble the four-centre transition state, or, alternatively, might indicate why the rate of transfer was so slow. Unfortunately it was not possible to obtain suitable crystals of any acyclic mixed anhydrides in order to compare the two situations.

A crystal of 39 was obtained from diethylether solution by slow evaporation of solvent under protection from atmospheric moisture, and the intensities of 1113 unique reflections out to $\theta = 25^{o}C$ measured on an Enraf Nonius CAD4 diffractometer by the ω-2θ scan method, using MoK_{α} radiation. The unit cell was determined by least squares refinement on the setting angles of 24 reflections ($16^{o} \leqslant \theta \leqslant 17^{o}$).
The crystal orientation was monitored during data collection, and three reference reflections were used periodically to check crystal stability. The data were corrected for Lorentz polarisation factors, and an empirical adsorption correction applied[105]. The phosphorus atom, as the heaviest atom, was located by a Patterson map, and the remaining non-hydrogen atoms by successive computation of difference maps, using the SHELX-76 program[106]. In the final least squares refinement cycle all non-hydrogen atoms were treated

anisotropically (anisotropic temperature factors, $T = \exp[-2\pi^2(U11h^2a^{*2} + U22k^2b^{*2} + U33l^2c^{*2} + 2U23klb^*c^* + 2U13hla^*c^* + 2U12kha^*b^*)]$).

At this stage, methylene and aromatic hydrogen atoms were placed geometrically, with all C-H bond distances fixed at 1.00Å, whilst the hydrogens on the N-substituted methyl group were treated as a rigid moiety. All hydrogen atoms were assigned a single isotropic temperature factor. In the final refinement a weighting scheme was applied. No attempt was made to determine the absolute structure of the crystal. Geometrical parameters were calculated by the program PARST[107] and molecular illustrations generated by PLUTO (Figures 11 and 12)[108]. Tables 11-18 give various cell parameters, atomic coordinates, anisotropic temperature factors and selected geometrical data. Observed and calculated structure factors, and an analysis of variance, are given in Appendix 1.

In most respects, the structure of <u>39</u> is similar to those determined for other oxazaphosphorinane systems: the heterocyclic ring itself is in the favoured chair conformation[86-88], as indicated by the ring data in Table 18[109], with the N-methyl substituent and phosphoryl oxygen atom in equatorial positions[88,91]. The benzoyloxy substituent is axial and almost perpendicular to the oxazaphosphorinane ring plane (Table 17), as is the bis(2-chloroethyl)amino substituent in cyclophosphamide[86]. The nitrogen atom is essentially sp^2 hybridised: the sum of the bond angles around N1 is 354.6° (Table 15), and the atom deviates only 0.205(3)Å from the plane defined by C1,P1

Figure 11: View of 39 along axis perpendicular to plane defined by P1-C1-C3 (indicating atom numbering scheme used).

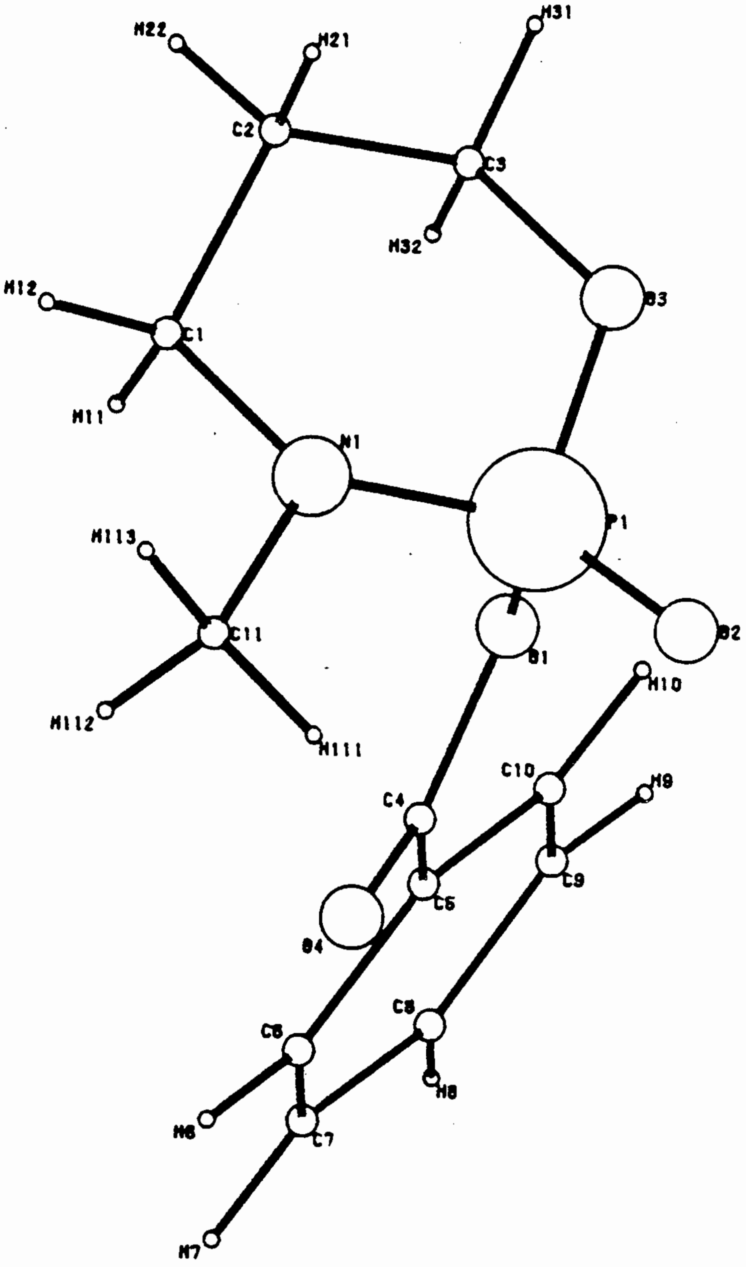


Figure 12: View of <u>39</u> along P1-C4 axis.

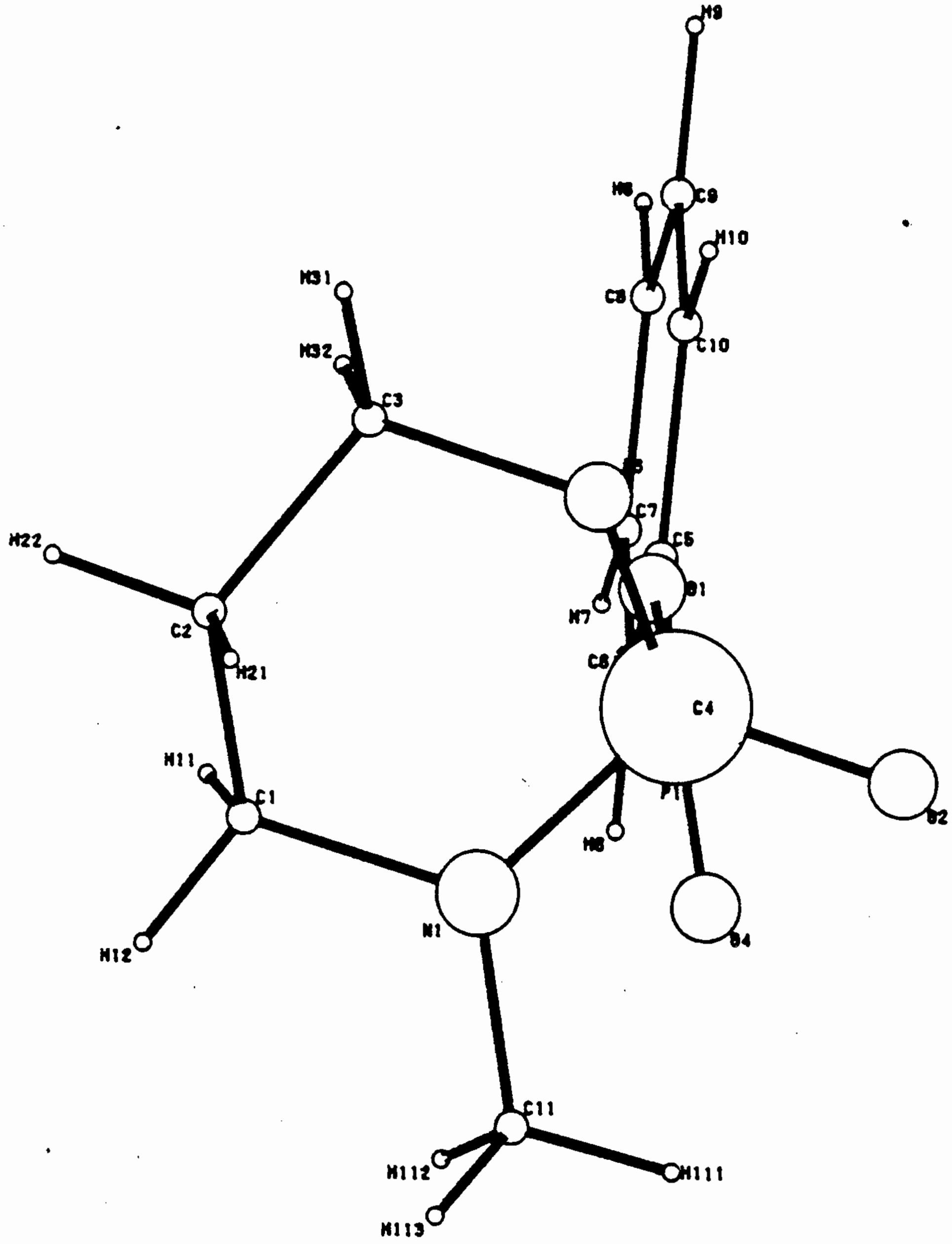


Table 11: Crystallographic data and experimental parameters for structure determination of 39.

Crystal data

molecular formula	$C_{11}H_{14}O_4NP$
molecular weight	255.21gmol^{-1}
space group	$Pna2_1$
a	22.229(6)Å
b	7.597(2)Å
c	7.210(2)Å
V	1217.6(6)Å^3
D_c for Z = 4	1.39gcm^{-1}
μ (MoK$_\alpha$)	2.21cm^{-1}
F (000)	536

Data collection

crystal dimensions	0.41 x 0.47 x 0.56 mm
scan mode	$\omega - 2\theta$
scan width	$(0.83+0.35\tan\theta)^{\circ}$
aperture width	$(1.30+1.05\tan\theta)$mm
aperture length	4mm
range scanned	1-25°inθ
number of reflections collected	1113
number of observed reflections (N) with I (rel) > 2σI (rel)	1037
average transmission for adsorption correction	98.2%

Final refinement.

number of variables (NP)	157
$R=\Sigma\|\|Fo\| - \|Fc\|\|/\Sigma\|Fo\|$	3.08%
$R_w=\Sigma w^{1/2}\|\|Fo\| - \|Fc\|\|/\Sigma w^{1/2}\|Fo\|$	3.05%
weighting scheme, w	$(\sigma^2F)^{-1}$
U (hydrogens)	0.076(3)Å^2
$S=(\Sigma w\|\|F_o\| - \|Fc\|\|^2/N-NP)^{1/2}$	2.28

Table 12: Fractional atomic coordinates of non-hydrogen atoms ($\times 10^4$; standard deviations in parentheses).

	x/a	y/b	z/c
P1	1578	120(1)	0
O1	982(1)	2402(3)	413(4)
O2	1606(1)	580(4)	-1892(4)
O3	2061(1)	2637(3)	501(4)
N1	1650(1)	-279(4)	1618(5)
O4	319(1)	198(3)	165(6)
C1	1730(2)	297(5)	3551(5)
C2	2216(1)	1684(5)	3691(6)
C3	2112(2)	3228(5)	2421(6)
C4	409(1)	1727(4)	407(6)
C5	-50(1)	3097(4)	704(5)
C6	-629(1)	2551(5)	1145(6)
C7	-1076(1)	3786(5)	1372(6)
C8	-951(2)	5556(5)	1161(6)
C9	-380(2)	6095(5)	718(6)
C10	73(2)	4873(5)	489(5)
C11	1385(2)	-2016(4)	1395(7)

Table 13: Fractional atomic coordinates for hydrogen atoms

(x 10^4; standard deviations in parentheses)

	x/a	y/b	z/c
H11	1341(2)	807(5)	3995(5)
H12	1841(2)	- 735(5)	4342(5)
H21	2610(1)	1132(5)	3370(6)
H22	2229(1)	2129(5)	4996(6)
H31	2454(2)	4075(5)	2534(6)
H32	1729(2)	3827(5)	2781(6)
H6	- 720(1)	1270(5)	1291(6)
H7	-1493(1)	3399(5)	1702(6)
H8	-1280(2)	6440(5)	1325(6)
H9	- 296(2)	7381(5)	572(6)
H10	488(2)	5268(5)	154(5)
H111	1305(2)	-2342(4)	74(7)
H112	1003(2)	-2090(4)	2123(7)
H113	1688(2)	-2845(4)	1932(7)

Table 14: Anisotropic temperature factors for non-hydrogen atoms ($10^3 Å^2$; standard deviations in parentheses)

	U11	U22	U33	U23	U13	U12
P1	44(1)	49(1)	43(1)	6(1)	7(1)	7(1)
O1	37(1)	45(1)	57(2)	1(1)	2(1)	4(1)
O2	71(1)	70(1)	46(2)	- 1(2)	9(1)	15(1)
O3	44(1)	62(2)	58(2)	14(1)	8(1)	- 4(1)
N1	54(1)	44(2)	57(2)	4(1)	3(2)	4(1)
O4	60(1)	43(1)	144(3)	-20(2)	10(2)	- 3(1)
C1	59(2)	64(2)	47(2)	7(2)	1(2)	0
C2	50(2)	86(3)	58(2)	1(2)	- 5(2)	- 5(2)
C3	52(2)	62(3)	76(3)	0	1(2)	-14(2)
C4	47(2)	48(2)	57(2)	-67(2)	1(2)	0
C5	40(2)	46(2)	40(2)	- 6(2)	3(2)	1(2)
C6	47(2)	52(2)	55(2)	- 5(2)	2(2)	- 8(2)
C7	38(2)	91(3)	56(2)	- 9(3)	5(2)	5(2)
C8	63(2)	70(3)	46(2)	- 7(2)	- 6(2)	29(2)
C9	78(3)	48(2)	53(2)	2(2)	3(2)	9(2)
C10	50(2)	43(2)	53(3)	- 1(2)	6(2)	- 2(2)
C11	90(3)	44(2)	76(3)	3(2)	9(2)	2(2)

Table 15: Selected geometric parameters (standard deviations in parentheses).

Bond lengths (Å)	
P1-O2	1.445(3)
P1-O1	1.636(2)
P1-O3	1.573(2)
P1-N1	1.628(3)
O1-C4	1.373(3)
N1-C11	1.454(5)

Bond angles (degrees)	
N1-P1-O1	109.5(1)
N1-P1-O3	104.3(1)
O1-P1-O3	97.1(1)
P1-O1-C4	122.9(2)
P1-N1-C1	119.0(3)
P1-N1-C11	120.5(3)
C1-N1-C11	115.1(3)

Torsion angles (degrees)	
N1-P1-O1-C4	-64.1(3)
P1-O1-C4-C5	-176.5(2)

Table 16: Equations of least-squares planes, and distances of specified atoms from planes (standard deviations in parentheses).

Plane 1	P1, C1, C11 $0.9503X + 0.2455Y - 0.1913Z = 3.1095$ N1 0.205(3)Å
Plane 2	C5, O4, O1 $0.0549X - 0.1537Y + 0.9866Z = 0.1332$ C4 0.005(4)Å
Plane 3	C5, C6, C7, C8, C9, C10 $0.2212X + 0.0658Y + 0.9730z = 0.6229$

Table 17: Angle between normals to least-squares planes

(standard deviations in parentheses)

	angle (degrees).
Plane 1 - Plane 2	95.7(2)
Plane 1 - Plane 3	90.5(2)
Plane 2 - Plane 3	164.2(2)

Table 18: Puckering Co-ordinates and Asymmetrical Parameters for Oxazaphosphorinan Ring.

(standard deviations in parentheses)

Asymmetry parameters

O3-P1-N1-C1-C2-C3

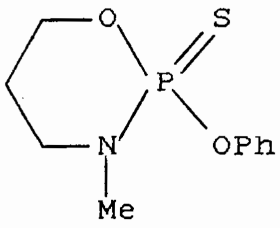
q_2 = 0.073(3)Å
q_3 = 0.502(3)Å
φ_2 = -96(3)°

Total puckering amptitude

QT = 0.508(3)Å
θ_2 = 8.3(3)°

ΔC_s(O3)	0.054(2)	ΔC_s(O3-C3)	0.279(1)
ΔC_s(P1)	0.022(2)	ΔC_s(P1-O3)	0.280(1)
ΔC_s(N1)	0.032(2)	ΔC_s(N1-P1)	0.282(1)
ΔC_2(O3)	0.220(1)	ΔC_2(O3-C3)	0.041(1)
ΔC_2(P1)	0.223(1)	ΔC_2(P1-O3)	0.036(1)
ΔC_2(N1)	0.221(1)	ΔC_2(N1-P1)	0.008(1)

and C11 (Table 16). All of the bond lengths are comparable with those in other, similar structures, except the P1-O1 anhydride bond, which is significantly longer than the P-O ester bond reported for N-methyl-2-phenoxy-2-thio-1,3,2-oxazaphosphorinane (<u>43</u>), 1.636(2)Å vs 1.605(2)Å[110].

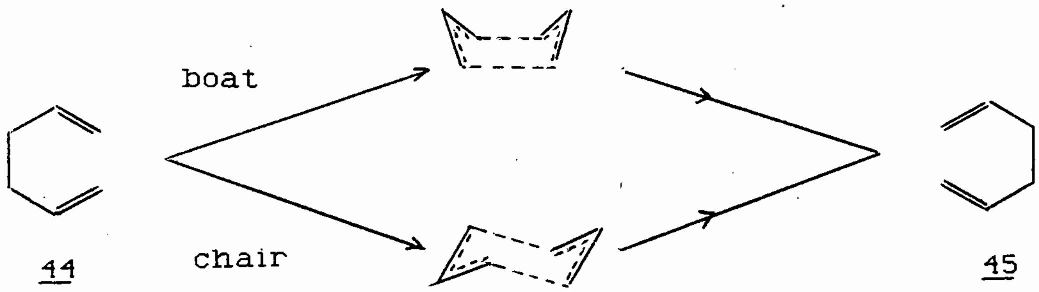


<u>43</u>

This arises from the greater electronegativity of the benzoyloxy group relative to the phenoxy group, which also causes that substituent to take up the axial position on the ring, normally favoured by phosphoryl oxygen atom.

In order to form the cyclic transition state required for intramolecular transfer, there must be a bonding interaction between the nitrogen lone pair of electrons, situated in a p orbital, and unoccupied orbitals at the carbonyl centre: in the solid state, the distance between the reacting N1 and C4 atoms is 3.270(4)Å, much greater than the interaction distances of 2.0 - 2.6Å found in other systems by Dunitz[104,111], but not significantly larger than the sum of the van der Waal's radii of N and C (3.20 - 3.25Å[112]). In addition, significant rotation is required about the P1-O1 and O1-C4 bonds, since in the transition state, syn-periplanar orientation of the P1-N1 and O1-C4 bonds is required (NPOC torsion angle of 0^{o}), and the carbonyl group must lie in the same plane as the oxazaphosphorinane ring (POCC torsion angle of 90^{o}). In going from the solid state to transition state structure then, bond rotations of $64.1(3)^{o}$ and $86.5(2)^{o}$ respectively, about these two bonds are required in order to achieve the necessary bicyclo [4,2,0]-octane fused ring system. During rotation it is possible that the axial hydrogens H11 and H32 on the oxazaphosphorinane ring and the carbonyl oxygen or aromatic hydrogens could come into close contact, resulting in steric hindrance, an increase in the energy required for transition state formation, and hence a decrease in reaction rate. To investigate this possibility, molecular mechanics calculations were carried out on 39.

The Molecular Mechanics Method (also known as the Force-field or Westheimer Method) of obtaining molecular information differs from molecular orbital calculations (Chapter 3) in that it considers, on the basis of the Born-Oppenheimer approximation, just nuclear motions, although electronic effects are taken into account. By considering the molecule as a rigid series of masses (atoms) linked by springs (bonds), and knowing the various force constants for stretching and bending movements (the force-field), it is possible to determine both the structure and energy of any molecule. Bond lengths and angles, and torsional angles can also be obtained and, most importantly, quantitative information about steric effects[113]. Different force-fields and methods of calculation have been developed to study a variety of systems: the conformation of cycloalkanes[114], the hydroxymethylene ketone-aldo enol equilibrium[115], and a conformational analysis of polyamino acids[116]. Simonetta *et al* have used this technique in discussing crystal structures[117], and in obtaining support for the proposal, based on experimental results that the Cope rearrangement of diallylic systems proceeds via an activated complex in which the molecule is in either a chair- or boat-like configuration, depending on the nature of substituents (Equation 25)[118].

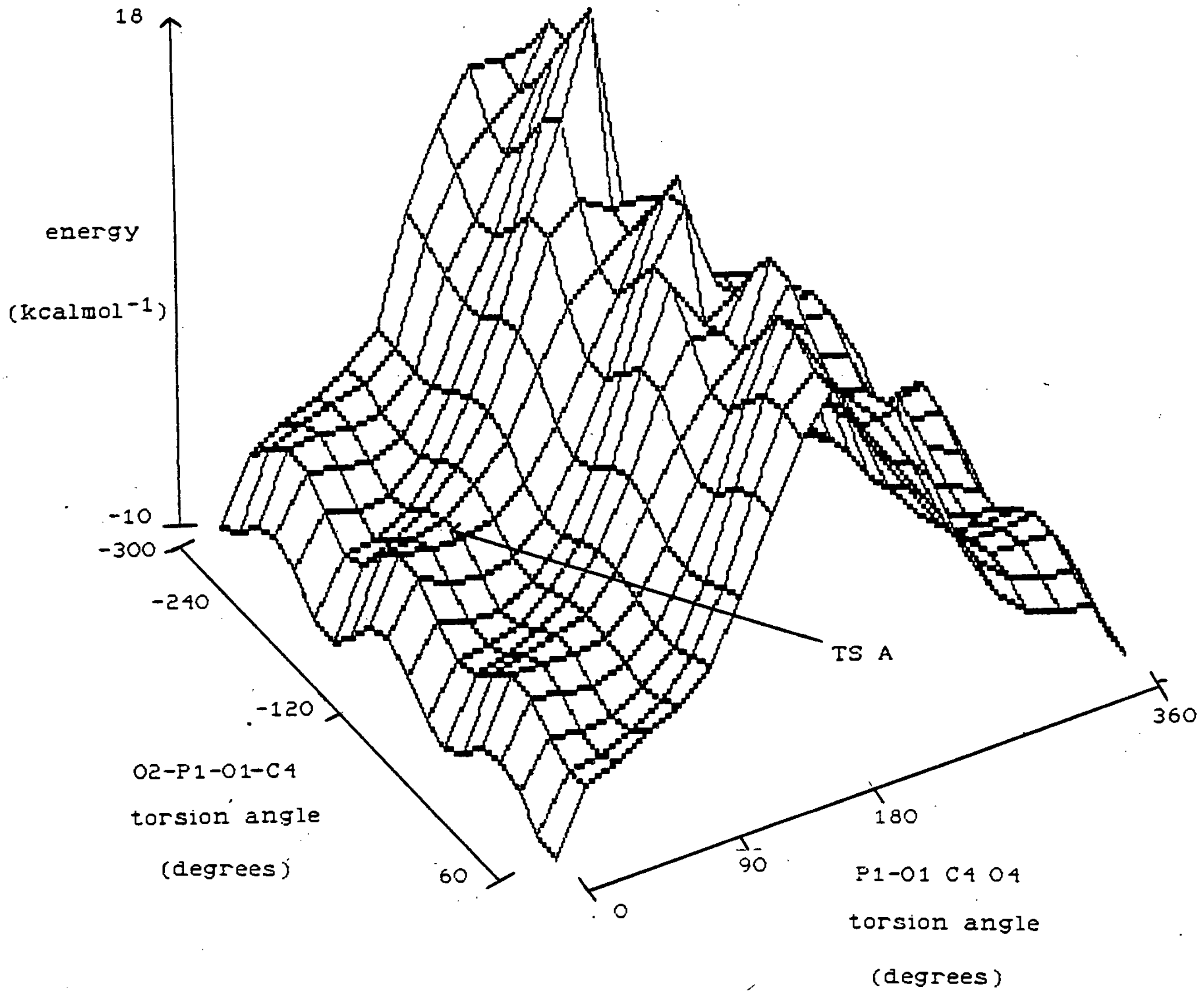


(25)

Their calculations ranged over the entire course of reaction (44 → 45) and energies, bond distances and bond angles in structures approximating the activated complex structures were calculated, at increments of 0.1 units along the reaction coordinate of 1 unit, by minimising the energy of the molecule after varying three parameters (related to dihedral angles between orbitals and atomic planes), whilst keeping other geometric values constant.

For our purposes, we used a similar approach. Starting from the conformation of 39 found in the solid state, a potential energy surface (Figure 13) was generated by driving the O2-P1-O1-C4 and P1-O1-C4-O4 torsional angles over their full range

Figure 13: Potential energy surface for <u>39</u>.



in steps of 20^{0}; at each stage complete geometric optimisation was allowed. The calculations were performed with a program developed in these laboratories[119] and Allinger's MM2(80) force-field[120], updated with the constants given in Appendix 2. The partial charges given by Weiner et al[121] were used to calculate bond moments. The addition of lone pairs on oxygen and nitrogen atoms was omitted since their inclusion resulted in poor N-P and O-P bond lengths. Figures 14 and 15 show the two conformations of <u>39</u> closest to the expected transition state structure (Figure 14: TSA, O2-P1-O1-C4 angles, -240^{0}; P1-O1-C4-O4 angle, 90^{0}; Figure 15: TSB, O2-P1-O1-C4 angle, -240^{0}; P1-O1-C4-O4 angle, -90^{0}); the approximate position on the energy surface of TSA is indicated on Figure 13. Table 19 shows the calculated energies of the three conformations, and Table 20 the calculated distances between those atoms considered most likely to interact sterically with each other.

Figure 13 indicates that TSA lies on or near a local energy maximum: because of the sampling method used and the approximate nature of the axes indicated, it is not possible to pinpoint the exact position of TSA on the energy surface. Additionally, TSA (or B) is not necessarily the exact transition state. Finally, because the method used allowed the complete geometric optimisation of the remainder of the molecule, and therefore minimisation of steric energies, it is probable that the surface is flattened somewhat compared to a real situation, and energy maxima and minima are less

Figure 14: TSA; O2-P1-O1-C4 torsion angle of -240^{0}; P1-O1-C4-O4 torsion angle of 90^{0}.

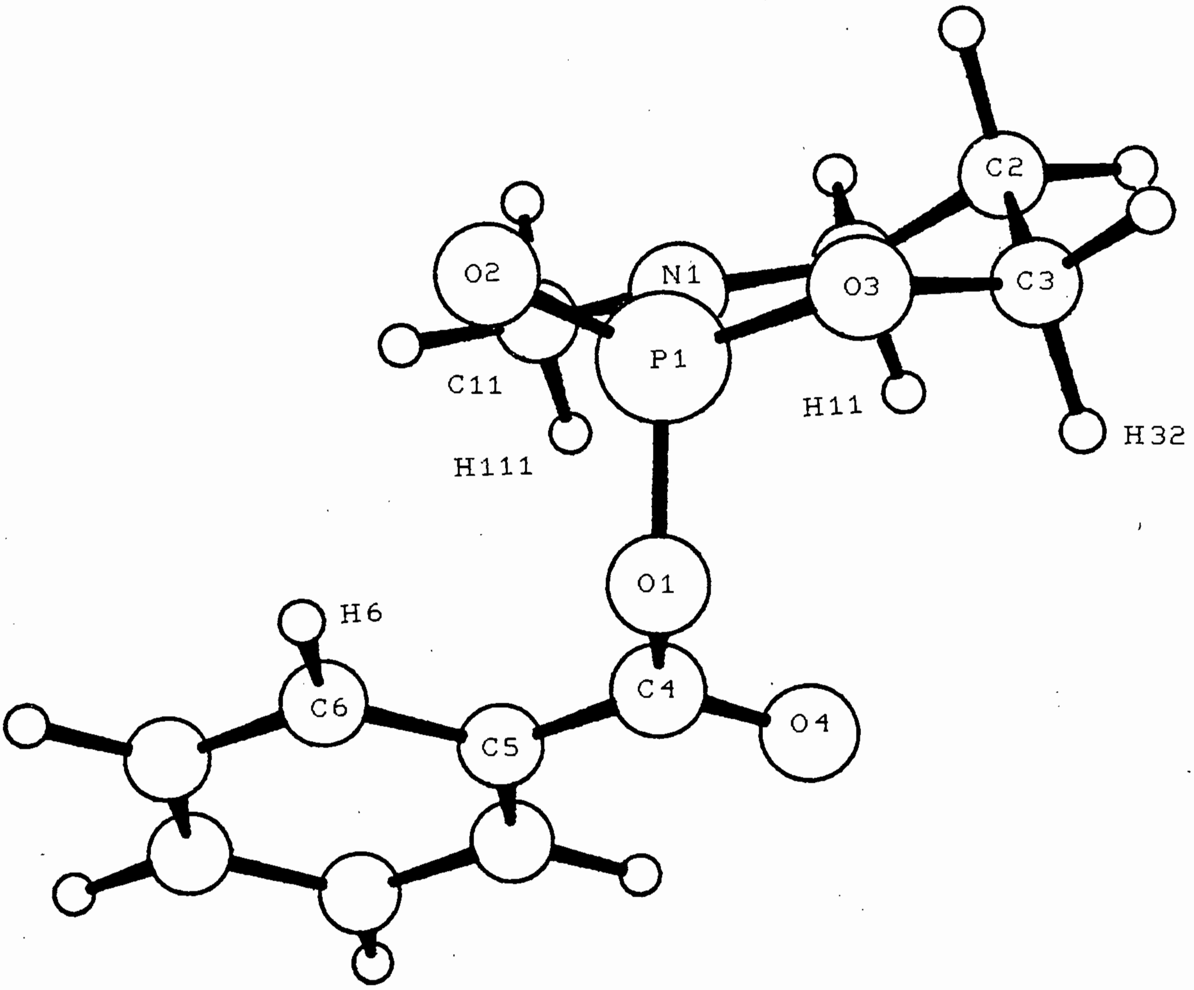


Figure 15: TSB; O2-P1-O1-C4 torsion angle of -240°; P1-O1-C4-O4 torsion angle of -90°.

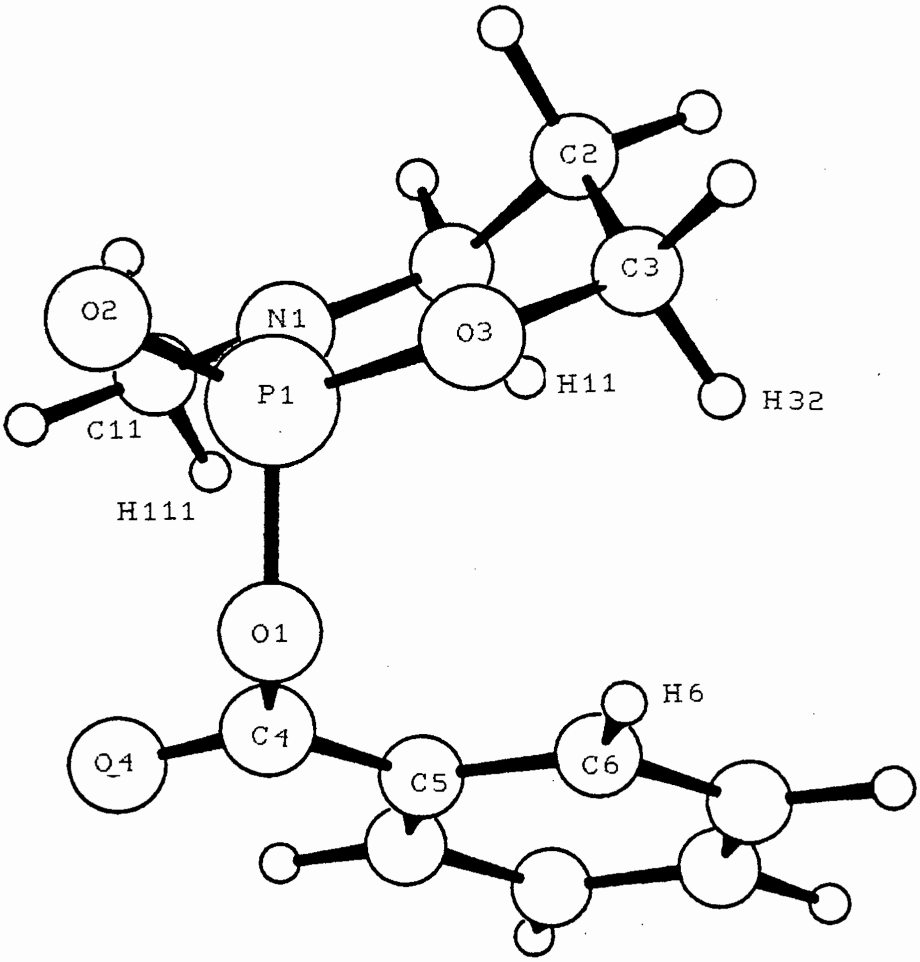


Table 19: Calculated energies for 39 and transition state-like conformers.

	E_{TOTAL} (kcalmol^{-1})	ΔE_{TOTAL} (kcalmol^{-1})
39	-10.2464	-
TS A	- 3.5230[a]	+ 6.7234
TS B	- 3.5440[b]	+ 6.7024

[a] average energy for conformers with P1-O1-C4-O4 angles of 80° and 100°.

[b] average energy for conformers with P1-O1-C4-O4 angles of -80° and -100°.

Table 20. Calculated interatomic non-bonded distances (Å)

TS A		Σ van der Waal's radii	
H11-O4	2.9486	H-O	3.24
H32-O4	3.2463		
H111-H6	2.8857	H-H	3.00[a]
N1-C4	2.9928	N-C	3.20-3.25[b]
TS B			
H111-O4	2.7532		
H32-H6	2.3936		
N1-C4	3.0034		

[a] Ref 119;
[b] Ref 112.

pronounced. The very high energy points in Figure 13 arise from those conformations in which the benzene ring is directly underneath the oxazaphosphorinane ring, a situation in which a great deal of steric interaction is to be expected.

The total energies calculated (Table 19) indicate that there is an energy increase of about 6.7 kcalmol^{-1} as 39 is twisted into conformation TSA or B. Much of this increase probably arises from the eclipsing of the P1-N1 and O1-C4 bonds, but it may be contributed to by steric interactions, particularly between H11 and O4, and H111 and H6 in TSA, or H32 and H6, and H111 and O4 in TSB. In these cases the calculated distances between atoms are less than the sum of the respective van der Waal's radii (Table 20). The C4 and N1 atoms in both conformations are also close enough for orbital overlap to occur. Once again, it should be noted that because of the optimisations allowed, TSA and TSB represent the most energetically stable situations possible, for which the geometric relationship between the P1-O1 and O1-C4 bond is specified, and the calculated energy values are probably lower than in reality.

In previous work (Chapter 3; ref 76) a calculated activation energy difference of 11 kcalmol^{-1} was regarded as large enough to account for the fact that only amino, and not alkoxy, groups were transferred in phosphoric-carboxylic anhydride systems. In the case of the cyclic system 39 then, it seems likely that an energy requirement of 6-7 kcalmol^{-1}, arising from increased rotational and steric requirements, could result in a 50-fold decrease in rate compared to a more flexible acyclic system. For this to be proved, however, a similar quantitative analysis of an acyclic analogue is required for comparison. Until this has been obtained, the slow rate of nitrogen group transfer in a system such as 39 is best described in qualitative, more classical terms, namely that as expected, steric effects are important for reactions proceeding by highly organised transition states[54], and that reductions in conformational flexibility cause reductions in reaction rates.

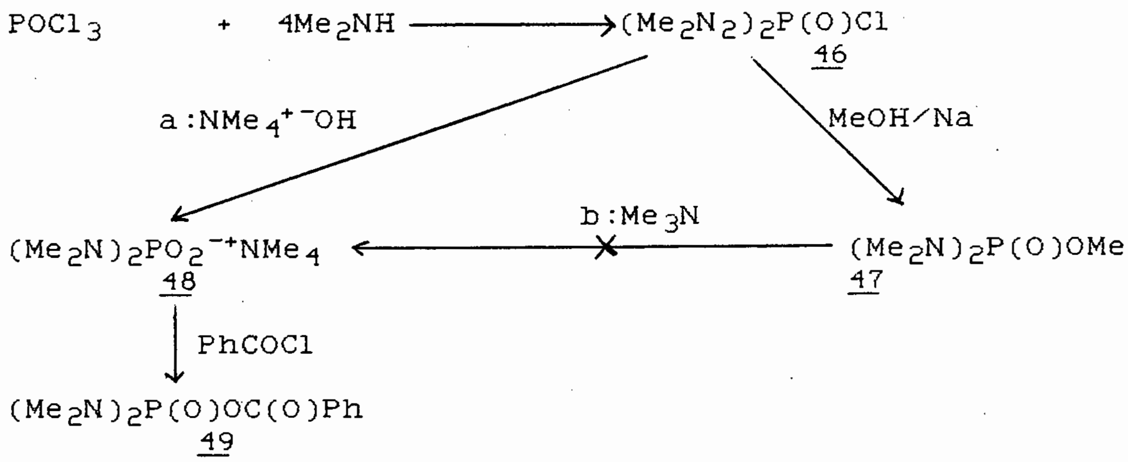
CHAPTER FIVE

REACTIVITY OF DIAMIDO SYSTEMS

5. REACTIVITY OF DIAMIDO SYSTEMS[31]

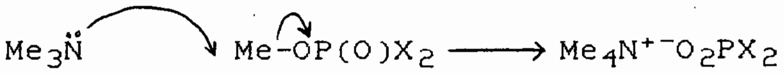
5.1 Introduction

As part of the study into the generality of amino group transfer from phosphoryl to carbonyl centre in mixed phosphoric-carboxylic anhydride systems, substrate 49 was prepared from the tetramethylammonium salt of N,N,N',N'-tetramethylphosphorodiamidic acid 48, according to the pathway outlined in Scheme 14.



Scheme 14

The alternative route to 48 from ester 47 could not be used as it proved difficult to obtain the salt in good yields using Me_3N as demethylating agent. A comparative study made at this time indicated that under identical conditions methyl N,N,N',N'-tetramethylphosphorodiamidate 47 was at least 10 times less reactive towards trimethylamine than trimethylphosphate (50), and 4 to 5 times less reactive than the monoamides dimethyl N,N-dimethylphosphoramidate (1a) and dimethyl N-phenylphosphoramidate (1m) (Table 21). This reduction in reactivity is believed to originate in phosphorus to nitrogen dπ-pπ bonding[122] (Equation 26; $X = NR_2$) which increases the electron density at phosphorus and consequently decreases the electrophilicity of the carbon atom in the methoxy substituent, thus slowing down the demethylation reaction.



$$Me_3\ddot{N} \quad Me{-}OP(O)X_2 \longrightarrow Me_4N^{+\,-}O_2PX_2 \qquad (26).$$

Hydrolysis of the ester bond in 47 using aq.NaOH was considered, but regarded as impractical, as studies in our laboratory had shown[123] the reaction to be very slow, for the same reasons as above. Thus, direct tetramethylammonium salt formation by reaction between N,N,N',N'-tetramethylphosphorodiamidochloridate 46 and aq.$NMe_4{}^{+\,-}OH$ was chosen as the most viable route to 49. When heated in acetonitrile solution 49 yielded N,N-dimethylbenzamide as the only isolable and identifiable product.

5.2 Reactivity Studies

5.2.1 Solvent effects and activation parameters

Samples of 49 were prepared in four different solvents and the rate of $PhCONMe_2$ (4a) formation measured by ^1H nmr spectroscopy, since substrate and product signals could again be distinguished. The first order rate constants obtained are shown in Table 22.

Table 21: Comparative reactivity of 47,50,1a,m towards Me_3N

Substrate	% yield NMe_4^+salt[a]
50, $(MeO)_3PO$	100
1a $(MeO)_2(NMe_2)P(O)$	40
1m $(MeO)_2P(O)NHPh$	50
47 $(MeO)P(O)(NMe_2)_2$	10

[a] Substrate: Me_3N = 1:2 moles; MeCN, 80°C, 5h

Table 22: Rates of formation of 4a from 49; 45°C

Solvent	$10^6k_1(^{-1})$	r	$k_{rel}(1)$[a]	$k_{rel}(2)$[b]
CCl_4	3.50	0.983	1	5
$CDCl_3$	4.31	0.994	1.2	12
$(CD_3)_2CO$	5.97	0.985	1.7	6
CD_3CN	6.86	0.991	2.0	4

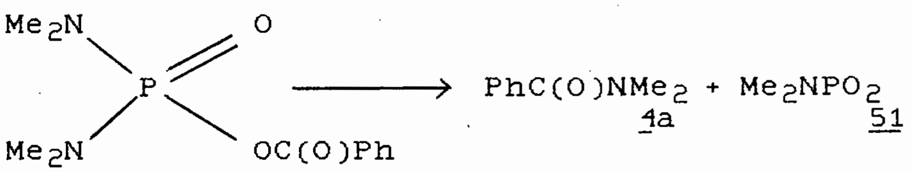
[a] $k_{rel}(1) = k_1(solvent)/k_1(CCl_4)$.

[b] Relative to $MeO(Me_2N)P(O)OC(O)Ph$(6a), after correcting to one NMe_2 group. i.e. k_1(4a)/k_1(6a).

Table 23: Activation parameters for formation of 4a from 49

Solvent units	E_a (kcalmol^{-1})	r	$\Delta H^\ddagger$ (kcalmol^{-1})	$\Delta S^\ddagger$ (calK^{-1}mol^{-1})
$CDCl_3$	13.3 ± 0.4	0.998	12.65 ± 0.4	-43.2 ± 2.2

As for 6a (Chapter 2), the variation in rate of nitrogen group transfer in 49 over a range of solvent polarities is small, approximately 12 times, but does follow the order of increasing solvent dielectric constants. It seems then that the mechanism of fragmentation in 49 is essentially the same as for 6a, giving rise to carboxyamide 4a and a metaphosphate species 51, but specific solvent effects play a smaller role (Equation 27). This diamido system is, however more reactive than the model system 6a, as reflected by the $k_{rel}(2)$ values, which take into account the statistical advantage existing for nitrogen group transfer in 49 by virtue of there being two migratory groups.



49

(27)

An increase in the reactivity of a system undergoing reaction by the same mechanistic pathway is often reflected in the energetics of the reaction. To this end, the rate of nitrogen group transfer in 49 was measured at two other temperatures, enabling a three point Arrhenius plot to be obtained, and hence the activation parameters shown in Table 23. Whilst the absolute values obtained are probably not accurate, since they are derived from a small data set, they should be valid for comparison with the values previously obtained for 6a.

The enthalpy of activation is less than the corresponding term for 6a (27.3 kcalmol^{-1}), and, if it were not for the large negative entropy term, this decrease in enthalpy alone might have accounted for the greater reactivity of the diamino system. The increased transition state ordering implied in this case is, we believe, related to the stereochemical requirements of the transfer reaction.

Molecular orbital calculations carried out on a model system of 6a indicated that a stereoelectronic effect in the transition state, involving the exocyclic oxygen substituent lone electron pair and the cleaving P-N σ bond, was important in determining the course of reaction (Chapter 3). In that instance, both lone pairs on oxygen were available for orientation into the required antiperiplanar arrangement, whilst in 49 the exocyclic group is a nitrogen substituent with only one lone pair of electrons. There must, therefore, be fewer favourable orientations, and so fewer conformations of the system as a whole, in which transfer of the other nitrogen group can occur. Such restrictions on conformation translate into decreased entropy in the transition state. The activation parameters thus do not adequately account for the greater reactivity of 49 over 6a, except to imply that, if the transition state did not have such high entropic requirements, then the observed enhancement might have been even greater.

It is more likely that the greater stability of the second product of reaction, the nitrogen substituted metaphosphate

51, compared to methylmetaphosphate, causes an increase in reactivity by providing the driving force for the reaction. A stable, crystalline diiminophosphorane 52, with phosphorus coordination number 3, has been isolated (Equation 28) and characterised by various methods, including ^{31}P nmr, which indicated a large downfield shift compared to iminophosphoranes of coordination number 4, and so an alteration in electron distribution[124].

$$R_2NP{=}NR + 2RN_3 \longrightarrow [R_2NP(NR)_2.N_3R] + N_2$$

$R = Si(CH_3)_3$

$$\longrightarrow R_2NP{\overset{\displaystyle =NR}{\underset{\displaystyle =NR}{}}} + RN_3 \qquad (28)$$

52

Since the corresponding oxygen systems cannot be similarly isolated and characterised (see Chapter 2), substitution of oxygen by nitrogen in such P(V), 3-coordinate systems obviously increases stability, but without reducing electrophilic reactivity, and so could account for the increased reactivity of 49 towards amino group transfer and formation of 4a.

5.3 Conclusion

Mixed phosphoric-carboxylic anhydrides derived from phosphorodiamidochloridates (e.g. 46) undergo a thermal phosphoryl to carbonyl migration of amino groups, to give carboxyamides, in a unimolecular process which is insensitive to changing solvent polarity, and which has a large, negative entropy of activation. However, reaction proceeds more rapidly than when there is only one migratory group present; this is attributed to a decrease in the energy requirements of the reaction as a whole by formation of a stabilised, nitrogen-substituted metaphosphate species <u>51</u>.

CHAPTER SIX

INTERMOLECULAR REACTIVITY OF MIXED ANHYDRIDE SYSTEMS

6. INTERMOLECULAR REACTIVITY OF MIXED ANHYDRIDE SYSTEMS

6.1 Introduction

Intermolecular reactions involving mixed anhydrides are predominantly those of attack of nucleophile at one or other of the acyl centres; these have been discussed earlier (see Chapter 1). However, during the course of investigation into the nature of amino group transfer from phosphoryl to carbonyl centre in mixed phosphoric-carboxylic anhydrides, results were obtained which we felt could be accounted for only in terms of intermediate disproportionation processes i.e. intermolecular reaction. In order to confirm the proposals, semi-quantitative kinetic studies were undertaken, the results of which are presented here.

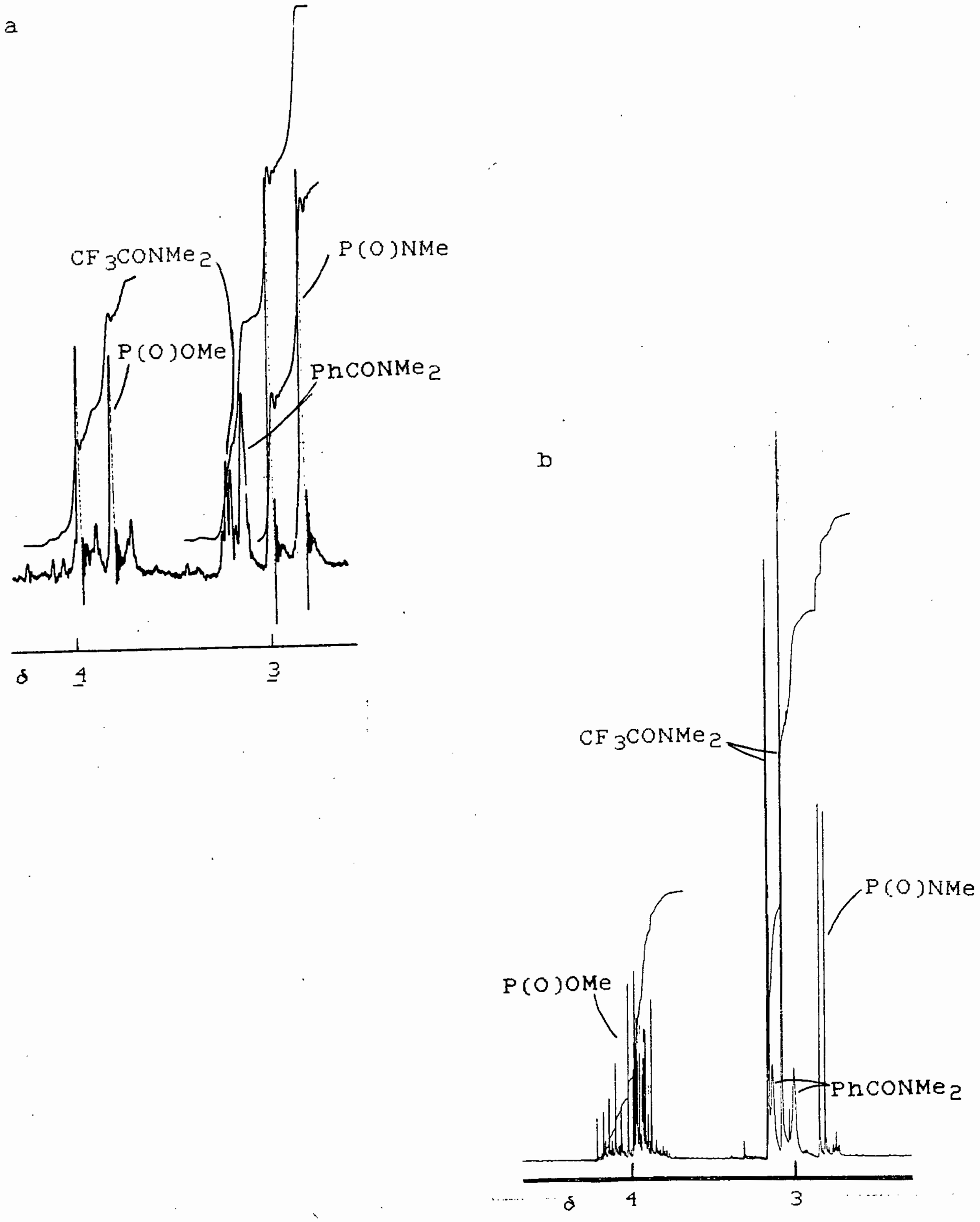
6.2 Disproportionation: role in nitrogen group transfer.

6.2.1 Effect of trifluoroacetic anhydride

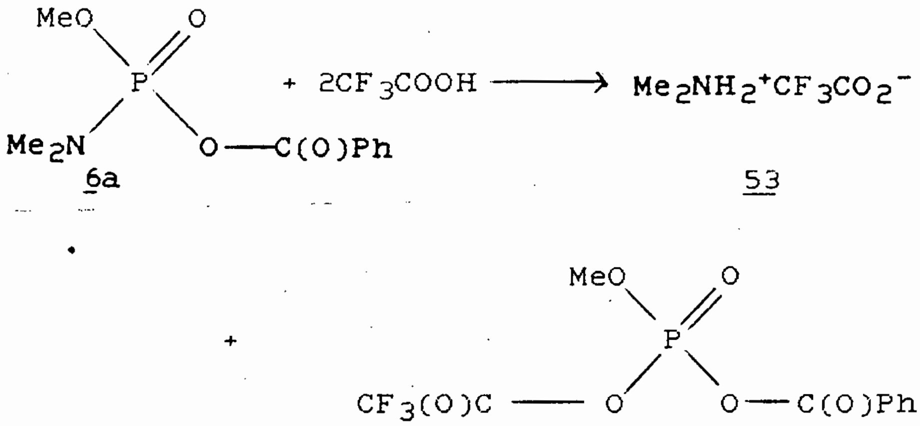
When the model mixed anhydride 6a was heated in $CDCl_3$ solution at 58°C in the presence of an equimolar amount of trifluoroacetic anhydride (TFAA), introduced as an expected Lewis acid catalyst, or when 6a was incubated in neat TFAA (refer Chapter 2, 2.3.5), a new product, apart from the expected N,N-dimethylbenzamide (4a), was observed. In the 60MHz ^1H nmr spectrum it was apparent after 21 and 3h heating, respectively, as a quartet at $\delta 3.20$ (Figure 16a). The possibility that this signal arose from a product formed by acid catalysed nucleophilic attack at 6a, as would occur if

Figure 16: ^{1}H nmr spectra of reaction mixtures resulting from heating of 6a and TFAA ($CDCl_3$).

a: 60 MHz spectrum
b: 300 MHz spectrum

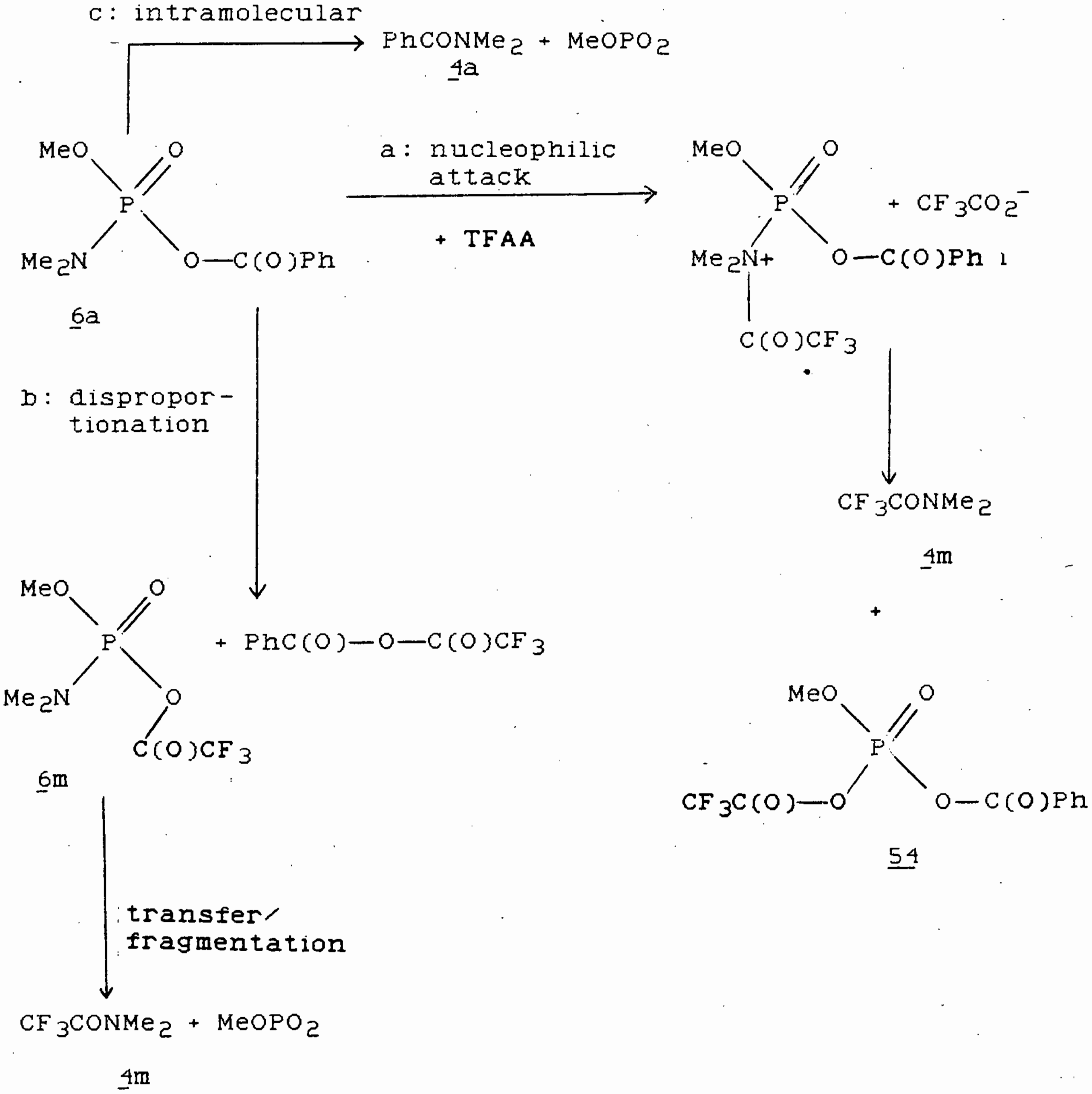


TFAA was hydrolsed to the free acid, (Equation 29), was investigated.



(29)

When 6a was dissolved in trifluoroacetic acid and heated, all substrate signals in the N-methyl region of the ^{1}H nmr spectrum rapidly disappeared, and were replaced by a triplet at δ3.0, characteristic of 53. This signal was upfield of substrate, whilst that arising from the unknown product was downfield, and the two signals had different multiplicity: obviously they did not correspond to the same compound. Another possibility was that the unknown species was N,N-dimethyltrifluoroacetamide (4m; $R = R^1 = Me$; $R^2 = CF_3$); formed either by direct transfer of the dimethylamino group from the carbonyl centre of TFAA (Scheme 15, route a), or by initial disproportionation of the two anhydrides to yield a new mixed anhydride (6m) within which intramolecular transfer of the nitrogen substituent occurred (route b).


c: intramolecular
PhCONMe2 + MeOPO2
4a
MeO
O
P
Me2N
O—C(O)Ph
6a
a: nucleophilic attack
+ TFAA
MeO
O
P
+ CF3CO2⁻
Me2N+
O—C(O)Ph
C(O)CF3
b: disproportionation
MeO
O
P
+ PhC(O)—O—C(O)CF3
Me2N
O
C(O)CF3
6m
transfer/ fragmentation
CF3CONMe2 + MeOPO2
4m
CF3CONMe2
4m
+
MeO
O
P
CF3C(O)—O
O—C(O)Ph
54

Scheme 15

To confirm that the unidentified product was 4m, this amide was synthesied by the Schotten-Baumann method (Equation 30)[42].

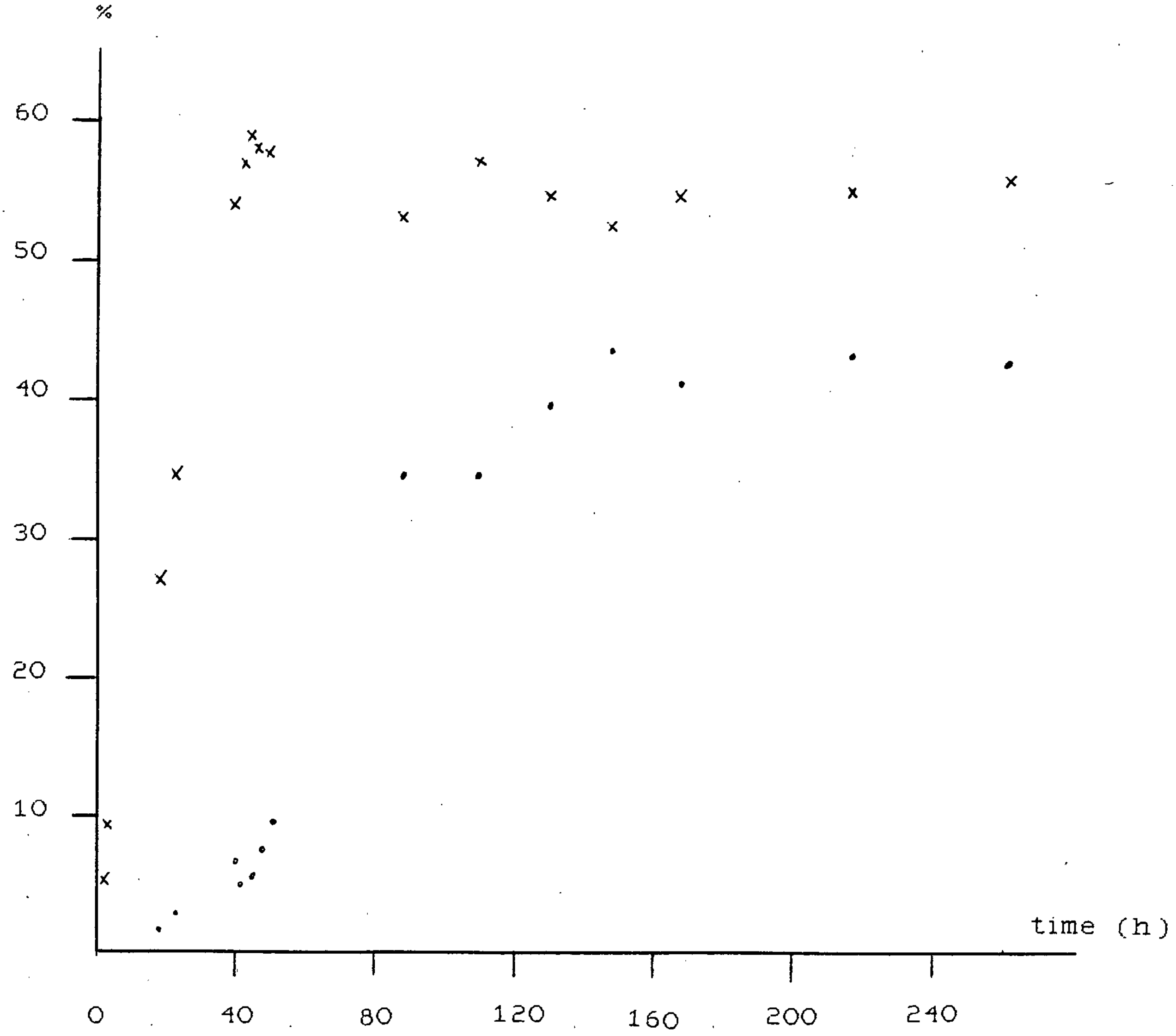
$$\text{TFAA} + 2\text{Me}_2\text{NH} \xrightarrow{\text{CH}_2\text{Cl}_2;\ 0^\circ\text{C}} \underset{\mathbf{4m}}{2\text{CF}_3\text{CONMe}_2} \qquad (30)$$

The 300 MHz ^{1}H nmr spectrum of the product showed two signals in the same region as that originally observed (δ3.06, d; δ3.15 q), corresponding well with literature values[125] for 4m; the splitting pattern arises from long-range coupling between two non-equivalent N-methyl groups and the fluorine substituents.

Repetition of the reaction between equimolar amounts of 6a and TFAA in $CDCl_3$ at 70°C, now using 300 MHz ^{1}H nmr spectroscopy to examine the reaction mixture at intervals, showed a decrease with time in substrate signal intensity, and a concurrent increase in intensity of signals corresponding to 4a, and at δ3.06 (doublet) and δ3.15(quartet) i.e. corresponding to 4m (Figure 16b). Figure 17 shows the extent of formation of both products during the course of reaction. 6a is converted almost equally to 4a and 4m, but initial formation of 4m is more rapid.

Reactions of the type shown in route a (Scheme 15) are known to result in carboxyamide formation during N-acylation of phosphoramidates by acyl halides, under neutral and basic conditions[53,6]. Challis and Iley have also shown that

Figure 17: Extent of 4a (.) and 4m (x) formation with time (from 6a; 70°C; $CDCl_3$).



tertiary phosphoramidates 55a,b react rapidly with TFAA at 25°C to yield 4m (Equation 31)[63].

$$X_2P(O)NMeR + TFAA \longrightarrow 4m + X_2P(O)OC(O)CF_3 \qquad (31)$$

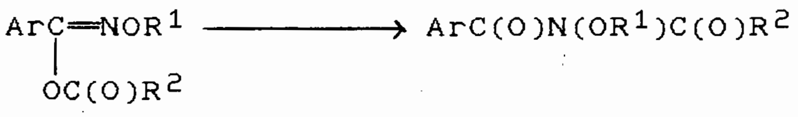
55 a, X = EtO; R = Me
b, X = NMe_2; R = Me
c, X = EtO; R = H

55c reacted with TFAA to yield initially the mixed phosphoric-carboxylic imide (initial $k_2 = 5.2 \times 10^{-3} M^{-1} s^{-1}$), and similar results were obtained for reaction with trichloroacetic and chloroacetic anhydrides. In all cases, imide formation was followed by rapid P-N bond cleavage and carboxyamide formation. In view of this rapid bond cleavage, it is however unlikely that route a accounts for formation of 4m from 6a in our case: the slower, intramolecular transfer reaction (route c; $k_1 = 5.1 \times 10^{-6} s^{-1}$ at 70°C; obtained previously (Chapter 2)), would not be able to compete with this faster, bimolecular process to the extent where almost 50% of substrate was converted to 4a, as observed. Another possibility, that formation of 4m occurred by reaction between 4a and TFAA after intramolecular transfer of the amino group was excluded when the ^1H nmr spectrum showed no change after prolonged heating of a solution of 4a and TFAA in $CDCl_3$. Route b thus appeared to be the most likely means by which 4m could be formed in this system.

The product of the proposed disproportionation reaction (6m) was independently synthesised on an nmr scale and allowed to fragment *in situ*, the reaction mixture remaining at 50°C in the 300 MHz nmr spectrometer probe (Equation 32).

$$\begin{tikzcd} \mathrm{TFAA} + \mathrm{NMe_4}^{+}{}^{-}\mathrm{OP(OMe)NMe_2} \arrow[r, "\mathrm{CD_3CN}"] & 6\mathrm{m} + \mathrm{NMe_4}^{+}{}^{-}\mathrm{O_2CCF_3} \arrow[d, "50^{\circ}\mathrm{C}"] \\ & 4\mathrm{m} \end{tikzcd} \qquad (32)$$

Periodic monitoring by ^1H nmr spectroscopy over a period of 3h indicated that 6m decomposed to yield only 4m. The rate of formation of 4m followed first order kinetics, and a rate constant $k_1{}^1 = 1.48 \times 10^{-4}s^{-1}$ ($r = 0.9960$) was obtained. This is 71.5 times faster than the rate of formation of 4a from 6a ($k_1 = 2.07 \times 10^{-6}s^{-1}$; 50°C; CD_3CN). McCarthy and Hegarty observed that in the rearrangement of acyl-O-alkylbenzohydroximic anhydrides to N-acyl-N-benzoyl-O-alkyl-hydroxylamines (Equation 33) changing R^2 from a methyl to a phenyl group caused a reduction in rate of 5 times[71].



$$\underset{\displaystyle \mathrm{OC(O)R^2}}{\mathrm{ArC{=}NOR^1}} \longrightarrow \mathrm{ArC(O)N(OR^1)C(O)R^2} \qquad (33)$$

They accounted for this in terms of the increased steric requirements of the phenyl group in a four-membered transition state, and to the reduction in reactivity of aromatic acyl systems to nucleophiles compared to that of aliphatic acyl compounds. Given that amino group transfer in 6a or 6m also requires a four-membered transition state (Chapters 2-4), it is likely that the greater reactivity of 6m compared to 6a stems from the same factors, and is enhanced by the strongly electron-withdrawing nature of the fluorine substituents in 6m, which facilitates the approach of the amino group at the carbonyl centre.

The results obtained for the reaction of 6a and TFAA in $CDCl_3$ allow description of this reactive system in semi-quantitative terms, illustrated in Scheme 16.

$$\begin{tikzcd}
6a \arrow[r, "\substack{k_1\\ \text{unimolecular}}"] \arrow[dr, "\text{TFAA}", "\substack{k_2\\ \text{bimolecular}}"'] & 4a + [MeOPO_2] \\
 & 6m + PhC(O)OC(O)CF_3 \arrow[d, "\substack{k_1^1\\ \text{unimolecular}}"] \\
 & 4m + [MeOPO_2]
\end{tikzcd}$$

$k_1^1 \cong 71k_1$

Scheme 16

Since the ^1H nmr spectrum never gave any indication of the presence of 6m in the reaction mixture, its rate of disappearance, by amino group transfer and fragmentation, must be much faster than its rate of formation, i.e. $k_1^1[6m] >> k_2[6a][TFAA]$. A slow disproportionation step (6a→6m) would explain why 4a is formed in comparable quantities to 4m, in spite of the fact that fragmentation of 6m is much faster than that of 6a ($k_1^1 \cong 71k_1$).

At the initial stage of reaction, when the concentrations of 6a and TFAA are relatively high, the bimolecular reaction (6a→6m) proceeds at a considerable rate, so formation of 4m is significantly greater than that of 4a (Figure 17). As the concentrations of substrates decrease, the rate of formation of 4a (by a first order reaction) decreases less dramatically than that of 6m (formed by a second order reaction), and consequently the product ratio [4a]:[4m] gradually increases.

6.2.2 Formation of phosphorodiamidates from phosphoramidochloridates via amino group transfer.

Because our interest in the reaction involving transfer of nitrogen functional groups from phosphoryl to carbonyl centres originated with an observation made during a study of the reaction between phosphoramidate monoester monoanions and acyl chlorides, our approach to the synthesis of various intermediate mixed anhydride species 6 for kinetic experiments was always that shown in Equation 34.

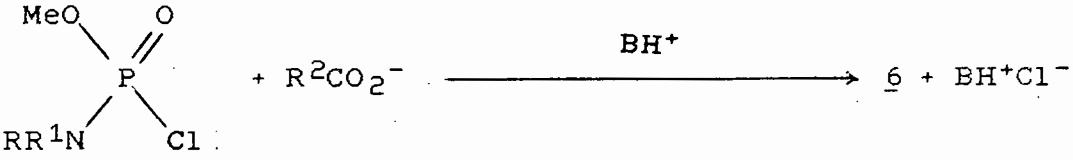
(34)

2

R,R^1 = H, alkyl, aryl; R^2 = aryl

6 a, $R = R^1$ = Me; R^2 = Ph

However, it is just as likely that 6 will be formed by reaction between the phosphoramidochloridate and carboxylic acid (Equation 35):

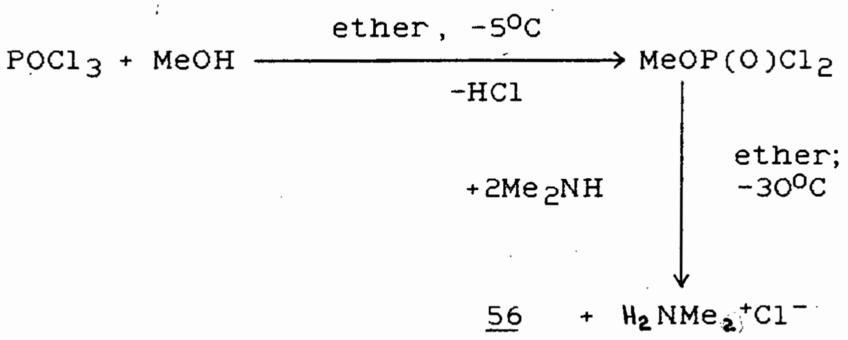


(35)

56

and in fact this is the usual route to mixed phosphoric-carboxylic anhydrides for use in anhydride, amide or ester synthesis[15,17,126]. Our attempt to synthesise 6a by this latter route proved difficult, and in addition an unexpected product was obtained.

Several attempts were made to synthesise 56 ($R = R^1 = Me$) from N,N-dimethyl phosphoramidodichloridate and either methanol or methoxide ion, all of which yielded complex product mixtures arising from simultaneous mono- and disubstitution. 56 was eventually synthesised according to the procedure outlined in Scheme 17, but we still failed to obtain the product in a pure state: there was always 10-20% $H_2NMe_2{}^+Cl^-$ present.



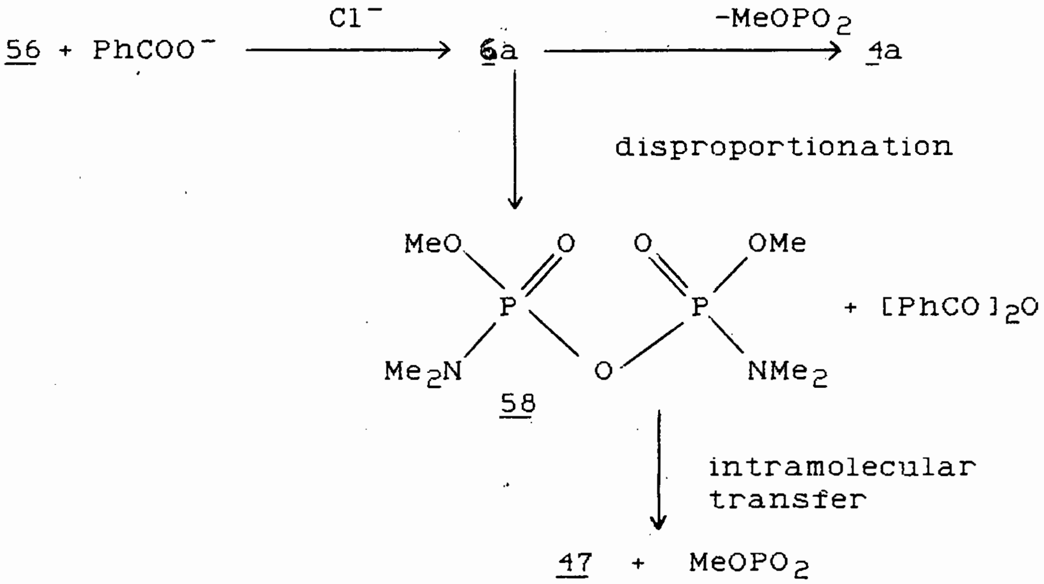
Scheme 17

The impure 56 obtained was reacted with benzoic acid in the presence of dimethylformamide and triethylamine (Equation 36)[127].

$$\underline{56} + PhCOOH + DMF \xrightarrow[\text{6:1 MeCN: ether; 1h reflux}]{Et_3N} \underline{4a} + \underline{57} + HCl \qquad (36)$$

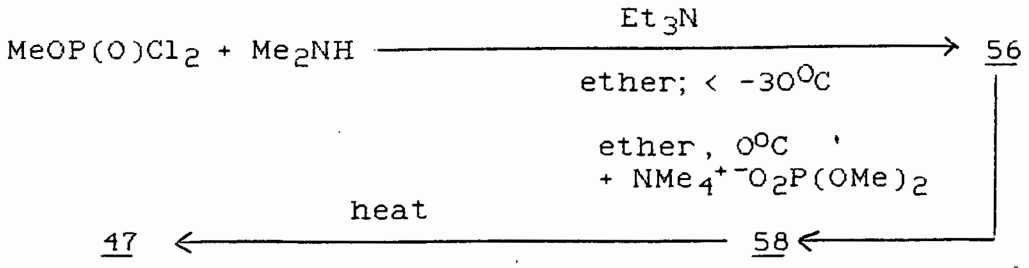
After 1h reflux the products were isolated by removal of solvents, and washed with water. The ^1H nmr spectrum showed the presence of N,N-dimethylbenzamide, and some other, phosphorus-containing species ($\delta2.66$, $\delta3.67$; two doublets; 4:1 ratio). There was no evidence for mixed anhydride 6a, but this species was probably hydrolysed on aqueous work up if still remaining. Separation of 4a and the unknown product 57 by column chromatography proved unsuccessful, but they could be separated by gas chromatography (57; t_R = 4.6min; 9%; 4a; t_R = 9.7min; 58%), and 57 was identified by comparison with authentic samples as methyl N,N,N',N'-tetramethylphosphorodiamidate, MeOP(O)(NMe$_2$)$_2$, i.e. 47.

As with formation of 4a and 4m, concurrent formation of 4a and 47 was thought to involve a competitive disproportionation process (Scheme 18).



Scheme 18

In order to test this possibility, anhydride 58 was independently prepared and heated for 195h at 70°C in $CDCl_3$, with periodic monitoring by ^1H nmr spectroscopy (Scheme 19).



Scheme 19

To achieve this, a more satisfactory synthetic route to 56, using triethylamine as base and carrying out the reaction at very low temperature, was developed.

Synthesis of 58 by controlled hydrolysis[128,129] yielded a non-distillable mixture, probably polymeric phosphates arising from hydrolysis of 58 itself.

After 74h heating, two new doublets were observed, in the ^1H nmr spectrum of the reaction mixture, corresponding to 47; these increased in intensity until after 195h 50% of the pyrophosphate diamide had been converted to phosphorodiamidate. Transfer of nitrogen functional groups in a symmetrical diacyl system such as 58 was thus shown to be possible, but the rate of transfer was slower than in 6a ($k_{rel} = 5$)$^+$. Assuming that the 9% 47 determined by gc analysis was formed entirely during the 1h reflux step, the rate of transfer in the pyrophosphate in the kinetic experiment was also slower than in the original synthetic

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$$^+k_1(\underline{58}) = \frac{\ln 1/1-x}{t} = 9.9 \times 10^{-7}s^{-1} \text{ for } x = 50\%,\ t = 195h;$$

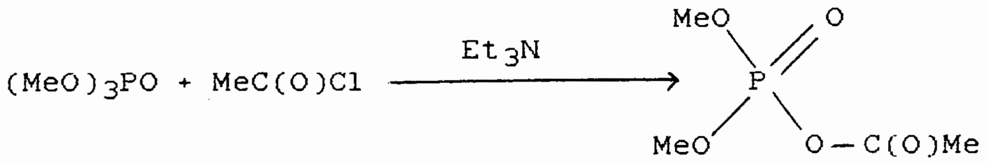
$$k_1(\underline{6a}) = 5.1 \times 10^{-6}s^{-1};\ k_{rel} = k_1(\underline{6a})/k_1(\underline{58})$$

experiment. However, the conditions under which the two reactions occurred were very different: 58 was reacted as the pure compound in neutral solution, whilst formation of 47 from 56 took place in the presence of acidic and basic species, and free chloride ion. It is possible that one or more of these species catalysed either the disproportionation or intramolecular transfer reaction.

It is worth noting that at no other stage of the kinetic work was there any indication of formation of products similar to 47 from disproportionation of mixed phosphoric-carboxylic anhydrides. Schradan and similar pyrophosphoramidates are known to be thermally stable[130], implying a reluctance of nitrogen-containing phosphate diacyl systems to undergo disproportionation.

6.3 Reactivity of acyl dialkyl phosphates

Part of our investigation into the reactions of phosphoramidate monoester monoanions with acyl chlorides involved determining whether the observed transfer of functional groups from phosphoryl to carbonyl centre was specific to amino groups, or extended to the transfer of alkoxy groups to yield carboxyesters. For this purpose, acetyl dimethylphosphate (59a) was synthesised by reaction between trimethyl phosphate and acetyl chloride in the presence of a catalytic amount of triethylamine (Equation 37)[36], yielding upon distillation 59a, but contaminated with trimethyl phosphate.



59a

(37)

Prolonged heating of this product mixture at 80°C gave no indication of methyl acetate formation, whilst a ^{1}H nmr spectrum run after 6 months' standing at room temperature indicated the additional presence of only the disproportionation products, acetic anhydride (60a) and tetramethylpyrophosphate (61). Benzoyl dimethylphosphate 59b, formed by reaction between dimethylphosphorochloridate and benzoic acid[127], also yielded 61 and benzoic anhydride 60b on distillation (Equation 10).

$$(\mathrm{MeO})_2\mathrm{P(O)OC(O)R} \longrightarrow 1/2[(\mathrm{MeO})_2\mathrm{PO}]_2\mathrm{O} + 1/2\ [\mathrm{RCO}]_2\mathrm{O} \qquad (38)$$

59 a, R = Me
b, R = Ph

61

60 a, R = Me
b, R = Ph

These findings were interpreted as confirming that transfer of ester functional groups from phosphoryl to carbonyl centre in a mixed anhydride system does not occur; a fully esterified system rather disproportionates to the symmetrical anhydrides.

Although mentioned in the literature[19,34,131] as a side reaction of mixed anhydride systems, usually observed on distillation, no systematic kinetic studies of disproportionation have been made. Having here a system which preferentially underwent disproportionation, we felt that it would be possible and worthwhile to obtain such kinetic information.

Fresh 59a was synthesised from the tetramethylammonium salt of dimethylphosphoric acid and acetyl chloride (Equation 39), it being easier to obtain pure 59a by this method than that used previously.

$$NMe_4{}^{+}{}^{-}O_2P(OMe)_2 + MeCOCl \longrightarrow \underline{59}a + NMe_4{}^{+}Cl^{-} \quad (39)$$

Solutions of the mixed anhydride substrate of known concentration (0.5-3.5M) were made up in different solvents ($CDCl_3$; CD_3CN; CCl_4) and heated (45; 50; 65; 70°C).
In all cases, two new signals were observed in the ^1H nmr spectrum soon after initiation of reaction (δ3.75, doublet; δ2.0, singlet), the intensities of which increased rapidly before attaining a maximum; thereafter, even on prolonged heating the system remained unchanged. It was not possible to obtain reliable rate data from these measurements.

Since it was not clear whether the new methoxy group doublet (δ3.75) arose from 61 (the disproportionation product) or dimethylphosphoric acid(62) formed by hydrolysis by traces of moisture, these compounds were synthesised (Equations 40 and 41) in order for comparisons to be made by ^{31}P nmr spectroscopy with a reaction mixture obtained after heating 59a for 64h at 60°C in $CDCl_3$ (Figure 18).

$$(MeO_2)P(O)Cl + (MeO)_3PO \xrightarrow{150^oC;\ 2h} \underline{61} \qquad (40)$$

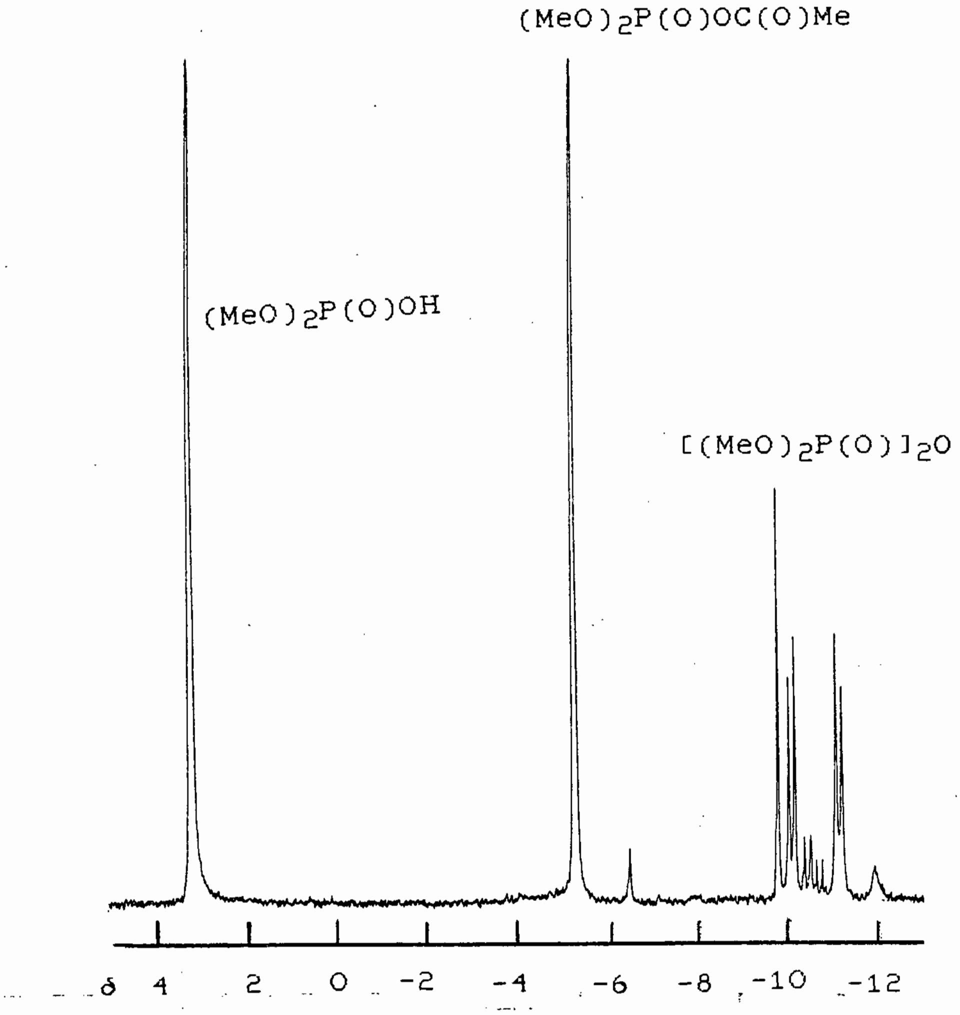
$$(MeO)_2P(O)Cl + H_2O \xrightarrow{18h\ stirring} \underset{\underline{62}}{(MeO)_2P(O)OH} \qquad (41)$$

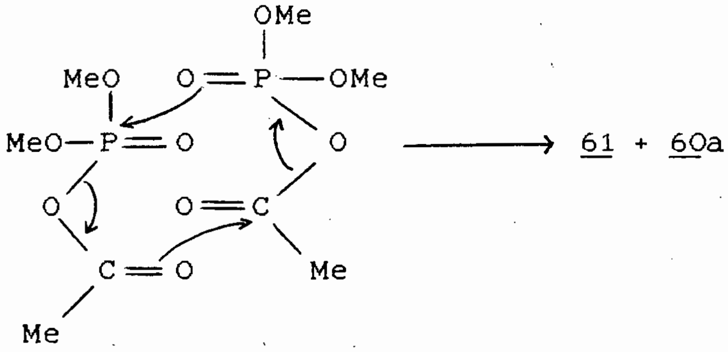
From the ^{31}P nmr spectrum it is seen that as well as pyrophosphate, there is other polymeric phosphate material, and a significant amount of hydrolysis product <u>62</u> present. We believe that the new signals in the ^1H nmr spectrum arise from the products formed on reaction of <u>59</u>a with residual water in the solvents, and that this is the predominant reaction occuring (Equation 42).

$$\underline{59}a + H_2O \longrightarrow \underline{62} + MeCO_2H \qquad (42)$$

Such a process could also account for the polyphosphate material observed, by reaction between <u>62</u> and <u>59</u>a, or <u>62</u> and itself. It seems therefore that in solution there is little or no disproportionation of acyl dialkyl phosphates, but rather reaction with any external nucleophile, followed by self-condensation. The reason for this may simply be a concentration effect: as a neat liquid <u>59</u>a can, upon heating (or distillation) become sufficiently reactive to disproportionate in a bimolecular fashion, as has been proposed (Equation 43)[23].

Figure 18: 300 MHz ^{31}P nmr spectrum of reaction mixture obtained from 59a (64h; 60°C; $CDCl_3$).





(43)

Upon dilution, the electrophilicity and the nucleophilicity of the respective centres in 59 may not be high enough to drive the system towards the (certainly entropically unfavourable) bimolecular disproportionation process.

6.4 Conclusion

The varying evidence for disproportionation processes in mixed phosphoric-carboxylic anhydrides discussed here indicate that the process is not as straightforward as it first appears, and is seemingly dependent on the reaction conditions and on the nature of the reacting diacyl species. Further work, encompassing the effects of acids, bases and free ions on the reaction, as well as concentration and substituents, may well allow the elucidation of a suitable mechanism for disproportionation.

CHAPTER SEVEN

CONCLUSION

7. CONCLUSION

The aim of this investigation into the functional group transfer reaction observed when phosphoramidic acid salts and acid chlorides were reacted together in neutral solution[5], and resulting in carboxyamide formation, was to establish the reasons for the apparent specificity of reaction, and to elucidate the reaction mechanism. Whilst similar processes had been observed[24,25] this study represents the first detailed, mechanistic investigation of the system, and incorporates a number of experimental and theoretical techniques available to the organic chemist.

Initial experiments indicated that only nitrogen-containing groups were transferred from the phosphoryl to carbonyl centre, regardless of the nature of the substituents at nitrogen or the type of acid chloride used; no carboxyester formation was ever observed. Reaction was shown to proceed with the initial formation of a mixed phosphoric-carboxylic anhydride, when benzoyl methyl N,N-dimethylphosphoramidate was isolated from a reaction mixture and yielded N,N-dimethylbenzamide on heating in solution. This mixed anhydride was used as a model in future experiments.

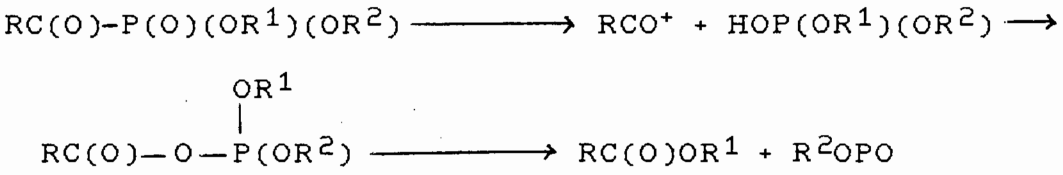
Formation of the carboxyamide obeyed first order kinetics, indicating an intramolecular transfer within the intermediate anhydride. From a series of solvent, temperature and substituent effect studies, using ^1H nmr spectroscopy to monitor the course of reaction, and in which only small rate variations were observed, it was concluded that the reaction was concerted and proceeded with formation of an isopolar, four-centre transition state. This was in part confirmed by a study involving conformational effects: linking the amino and alkoxy substituents at phosphorus into a six-membered ring system caused a large reduction in the rate of nitrogen group transfer. Molecular mechanics calculations indicated this arose partly from unfavourable steric interactions in the transition state. Similarly, the crystal structure determination indicated a solid state structure significantly different to that required in the transition state, unlike other cases with adjacent electrophilic and nucleophilic centres[104].

Further support for the proposed mechanism was obtained from MNDO molecular orbital calculations on a model system, which also provided an explanation for the specificity of reaction. Only one energy minimum was obtained when either nitrogen or oxygen substituent transfer was considered, this corresponding to a four-centre structure, but the activation energy of the transition state for oxygen group transfer was 11 kcalmol^{-1} greater than that for nitrogen group transfer. Analysis of the higher energy occupied orbitals revealed that in the latter case interactions giving rise to a stereoelectronic effect and causing P-N bond weakening were present; these were absent in the former transition state. Additionally, transfer of alkoxy groups was made unfavourable by the relatively lower nucleophilicity of the transferring oxygen atom than nitrogen atom, and by destabilising 1,3-orbital interactions.

Using N-methylaniline as a trapping agent, the other product of reaction, monomeric methylmetaphosphate, was identified. The large, negative entropy of activation observed for reaction in acetone was attributed to specific acid-base interactions between this electrophilic species and solvent, leading to adduct formation[60b] and increased molecular ordering in the transition state. An analogous effect, leading to rate enhancements, was believed to occur when Lewis acids were added: in this instance, the incipient carboxyamide complexed with the catalyst[65], so lowering the energy requirements for product formation and favouring the transfer process.

A mechanism involving specific, concerted, intramolecular nitrogen group transfer from phosphoryl to carbonyl centre in mixed phosphoric-carboxylic anhydrides is thus proposed; fragmentation to yield carboxyamide and monomeric methyl metaphosphate occurs *via* an isopolar four-centre transition state. It has recently been observed that in acidic media, acylphosphonic acids fragment with alkoxy group transfer to give carboxyesters and derivatives of phosphenous acid, HOPO[132]. Since quantum mechanical calculations indicate intermediate formation of dialkylphosphite and acyl cation, the possibility that transfer occurs within a mixed phosphorus-carboxylic anhydride, formed by recombination of the intermediates, is being investigated[133] (Equation 44).

Such a process would be directly analagous to the reaction investigated here.



$$RC(O){-}P(O)(OR^1)(OR^2) \longrightarrow RCO^+ + HOP(OR^1)(OR^2) \longrightarrow$$

$$RC(O){-}O{-}\overset{OR^1}{\overset{|}{P}}(OR^2) \longrightarrow RC(O)OR^1 + R^2OPO \qquad (44)$$

An alternative reaction available to mixed anhydride systems - disproportionation to the two symmetrical anhydrides, was also investigated, primarily because in some instances such a process was the only one which could account for the observed products. The systems considered gave varying evidence of the ease with which this supposedly facile and common reaction occurs[19,24].

In the presence of trifluoroacetic anhydride, benzoyl methyl N,N-dimethylphosphoramidate underwent competitive disproportionation to yield two new mixed anhydrides, the one of which (methyl trifluoroacetyl N,N-dimethylphosphoramidate) underwent rapid nitrogen group transfer to yield N,N-dimethyltrifluoroacetamide. Tetramethylpyrophosphate, on the other hand, was not observed when acetyldimethylphosphate was heated in solution for prolonged periods, although there was evidence for disproportionation when the mixed anhydride was distilled. Work done on dimethyl N,N,N',N'-tetramethylpyrophosphorodiamidate implied that its formation by disproportionation of benzoyl methyl N,N-dimethylphosphoramidate, and subsequent rearrangement to methyl N,N,N',N'-tetramethyl phosphorodiamidate, was influenced by the presence of ionic, acidic and basic species.

Since there have been very few[23] thorough studies of the disproportionation reaction, and in view of its apparent sensitivity to reaction conditions, it would be of interest to investigate this reaction in more detail, and in so doing expand on the already interesting and diverse chemistry of diacyl systems.

EXPERIMENTAL

EXPERIMENTAL

1) General

All solvents and commercial reagents were purified and dried by conventional methods before use. ^1H nmr spectra were recorded on Varian 60MHz EM360 or 200MHz XL200 and Bruker 80Mhz WP80, 90MHz WH90 or 300MHz AC300 spectrometers at the Universities of Cape Town and Pretoria, with TMS or DDS as internal standards. ^{31}P nmr spectra were recorded on the Varian 200MHz XL200 spectrometer at UCT and on a Bruker 500MHz WM500 spectrometer at the C.S.I.R., using H_3PO_4 or $(MeO)_3P(O)$ (TMP) as external standards. Aluminium-backed silica-gel plates (Merck, Kieselgel 60 F_{254}) were used for t.l.c., and silica-gel (Merck, Kieselgel 40) for column chromatography. Gas chromatography was performed on a Carlo Erba 4200 gas chromatograph, using a 2m-column packed with 3% silicone SE-30 on 100/120 mesh Gas Chrom Q, and He as carrier gas. The column was conditioned overnight at 190°C. Injection and detection (F.I.D.) temperatures of 250°C were used, and the internal standard was n-propyl benzoate. Analyses for C, H and N were carried out at U.C.T. and the C.S.I.R. The crystal structure was determined at U.C.T., M.O. calculations at Imperial College, London, and molecular mechanics calculations at Pretoria University.

2) SYNTHESIS OF REAGENTS AND SUBSTRATES

Methylphosphorodichloridate $MeOP(O)Cl_2$, 63

was synthesised by the addition of methanol to $POCl_3$. 71%. bp 66-70°C/22mm. ^1H nmr ($CDCl_3$): δ4.05 (d, J_{HP}16.9Hz).

Dimethylphosphorochloridate, $(MeO)_2P(O)Cl$, 64

was synthesised[134] from PCl_3, MeOH and SO_2Cl_2. 63%. bp. 45°C/2mm (lit. bp 55-57°C/2-3mm). ^1H nmr ($CDCl_3$): δ3.98 (d, J_{HP} 14Hz).

Dimethyl N-alkyl-and N,N-dialkyl-phosphoramidates, $(MeO)_2P(O)NRR^1$, 1.

1a, dimethyl N,N-dimethylphosphoramidate, $R = R^1 = Me$, was synthesised[35] by passage of excess Me_2NH through a solution of 64 (15.5g; 0.104 mol) in ether (150ml) at 0°C. Solids were removed by filtration, the filtrate washed with water (50ml) and solvent evaporated from the organic portion. 1a was obtained by distillation of the residue. 55%, bp 62°C/4mm (lit. bp 72°C/11mm). ^1H nmr ($CDCl_3$): δ 2.75 (6H, d, J_{HP} 10Hz, NMe_2); 3.72 (6H, d, J_{HP} 11Hz, OMe). Anal. calc. for $C_4H_{12}NO_3P$: C, 31.4; H, 7.8; N, 9.15%. Found: C, 30.7, H, 7.9; N, 8.9%.

Dimethyl N-alkylphosphoramidates were synthesised[135,136] by addition of the relevant amine (2 mol-equivalents) to 64 in ether, followed by filtration, washing of ethereal solution with water, and removal of solvent. ^{1}H nmr ($CDCl_3$): 1b, dimethyl N-ethylphosphoramidate, R = Et; R^1 = H: δ 1.12 (3H, t, J_{HH} 7Hz, Me); 2.97 (3H, m, CH_2 and NH); 3.66 (6H, d, J_{HP}11Hz, OMe); 1c, dimethyl N-isopropylphosphoramidate, R = i-Pr; R^1 = H; δ 1.18 (6H, d, J_{HH} 7Hz, 2 x Me); 3.30 (1H, m, CH); 3.69 (6H, d, J_{HP} 12Hz, OMe); 1d, dimethyl N-t-butylphosphoramidate, R = t-Bu; R^1 = H; δ 1.28 (9H, s, 3 x Me); 3.70 (6H, d, J_{HP}11Hz, OMe).

1e, dimethyl N,N-di-isopropylphosphoramidate, R = R^1 = i-Pr

a: A solution of 64 (5.0g; 35mmol) in benzene (20ml) was added to a stirred, cooled (10°C) solution of $NH(iPr)_2$ (3.5g; 35mmol) and Et_3N (4.0g; 40mmol) in benzene (80ml). After 4h stirring and overnight standing, precipitated solids were removed by filtration and solvent removed from the filtrate, yielding an oily mixture of products arising from both nucleophilic attack by secondary amine and demethylation by tertiary amine.

b: A solution of 64 (5.0g; 35mmol) in ether (15ml) was added slowly to a solution of $NH(iPr)_2$ (7.0g; 70mmol) in ether (100ml) at room temperature, and stirred for 4.5h. An additional amount of amine (5.0g; 50mmol) was then added and the solution refluxed for 2h and left standing overnight. After filtration and evaporation of solvent an oily mixture of products and substrates was obtained.

Attempts to purify this mixture by column chromatography were unsuccessful.

c: $NH(iPr)_2$ (20.2g; 0.20mol) was dissolved in ether (50ml) and added to a cooled solution of $POCl_3$ (15.1g; 99mmol) in ether (100ml). After 1h stirring, solids were removed by filtration, washed with ether and the combined filtrates washed with water (50ml). Removal of solvent from the organic phase yielded an impure mixture, containing hydrolysis products, which could not be purified.

Tetramethylammonium phosphates, $NMe_4{}^{+\,-}O_2P(OMe)NRR^1$, 2.

Ester 1 (13mmol) was dissolved in MeCN (8-10ml) and a standardised solution of Me_3N in MeCN (3-4 mol-equivalents) added. The mixture was sealed in a glass tube and heated at 80°C overnight. On cooling, the precipitated salt was separated by filtration, washed with cold MeCN, and dried and stored under vaccuum. 2a, R = R^1 = Me; 77%. ^1H nmr (D_2O): δ 2.60 (6H, d, J_{HP} 8Hz, NMe); 3.21 (12H, s, $NMe_4{}^+$); 3.51 (3H, d, J_{HP} 10Hz, OMe). Anal. calc. for $C_7H_{21}N_2O_3P$: C, 39.6; H, 9.9; N, 13.2%. Found: C, 39.05; H, 9.85; N, 14.3%.

2b, R = Et; R^1 = H; ^1H nmr (D_2O): δ 1.09 (3H, t, J_{HH} 7Hz, Me); 2.82 (2H, m, CH_2); 3.18 (12H, s, $NMe_4{}^+$); 3.45 (3H, d, J_{HP} 10Hz, OMe).

2c, R = i-Pr; R^1 = H, ^{1}H nmr (D_2O): δ 1.09 (6H, d, J_{HH}3Hz, 2 x Me); 2.88 (1H, m, CH); 3.15 (12H, s, NMe_4^+); 3.75 (3H, d, J_{HP}11Hz, OMe).

2d, R = t-Bu; R^1 = H; ^{1}H nmr (D_2O): δ 1.25 (9H, s, 3 x Me); 3.20 (12H, s, NMe_4^+); 3.70 (3H, d, J_{HP}11Hz, OMe).

Tetramethylammonium dimethylphosphate, $NMe_4^+O_2P(OMe)_2$, 64%. ^{1}H nmr (D_2O): δ 3.18 (12H, s, NMe_4^+); 3.55 (6H, d, J_{HP}11Hz, s, OMe).

N,N,N',N'-tetramethylphosphorodiamidochloridate, $(Me_2N)_2P(O)Cl$, 46 was prepared[137] by adding $POCl_3$ (55.1g; 0.36mol) in ether (240ml) to a cold (-30°C) solution of Me_2NH (69g; 1.53 mol) in ether (240ml) dropwise over 4h. After standing overnight, solids were removed by filtration, solvent evaporated and product obtained by distillation. 88%. bp 76°C/0.6mm. ^{1}H nmr ($CDCl_3$):δ 2.70 (d, J_{HP}13Hz). Anal. calc. for $C_4H_{12}ClN_2OP$: C, 28.15; H, 7.0; N, 16.4%. Found: C, 28.8; H, 7.4; N, 16.8%.

Methyl N,N,N',N'-tetramethylphosphorodiamidate, $(Me_2N)_2P(O)OMe$, 47 was prepared[138] by adding a solution of 46 (15.5g; 90mmol) in MeOH (130ml) to a solution of Na (2.1g; 90mmol) in MeOH (80ml). After completion of addition, the mixture was refluxed for 0.5h, cooled, solids filtered off and washed with MeOH, and filtrates combined.

The residue after removal of solvent was redissolved in $CHCl_3$ (130ml) and washed with water (2 x 25ml; 1 x 10ml). Product was obtained by distillation after removal of solvent. 44%. bp 46-48°C/0.5mm. ^1H nmr ($CDCl_3$): δ 2.65 (12H, d, J_{HP}10Hz, NMe_2); 3.60 (3H, d, J_{HP}11Hz, OMe). Anal. calc. for $C_5H_{15}N_2O_2P$: C, 36.1; H, 9.0; N, 16.9%. Found: C, 34.7; H, 9.0; N, 15.9%.

Tetramethylammonium N,N,N',N'-tetramethylphosphorodiamidate, $NMe_4^{+}\,{}^{-}O_2P(NMe_2)_2$, 48 was synthesised by the addition of 46 (3.78g; 22mmol) to a cooled solution of $NMe_4^{+}OH^{-}$ (17ml, 2.5% aq. solution; 70mmol). After 3h,water was removed by evaporation and azeotropic distillation with benzene to yield a crystalline, hygrosopic solid (equimolar 48 and $NMe_4^{+}Cl^{-}$). 99%. ^1H nmr (D_2O): δ 2.5 (12H, d, J_{HP}10Hz, NMe); 3.10 (24H, s, 2 x NMe_4^{+}). Anal. calc. for $C_{12}H_{36}N_4O_2PCl$: C, 43.0; H, 10.8, N, 16.7%. Found: C, 42.5; H, 11.1; N, 15.7%.

Dimethyl N-methyl-N-arylphosphoramidates, $(MeO)_2P(O)NMeAr$, 1 i-l.

Dimethyl N-methyl-N-phenylphosphoramidate, 1i; dimethyl N-methyl-N-(p-methoxyphenyl)-phosphoramidate, 1j were synthesised by adding 64 in benzene to a solution of the corresponding aniline 18(1.5 mol-equivalents) and Et_3N (1.1 mol-equivalents) in benzene. After 3h stirring at 0°C and overnight standing solids were removed by filtration, and the filtrate washed with aq. KOH solution (3 x 15ml; pH 9).

The organic portion was dried over $MgSO_4$ and solvent evaporated yielding 1i and 1j as oils.

1i, Ar = Ph; 42%. ^1H nmr ($CDCl_3$): δ 3.22 (3H, d, J_{HP}9Hz, NMe); 3.77 (6H, d, J_{HP}11Hz, OMe); 6.55-7.50 (5H, br s, Ph).

1j, Ar = p-MeO-C_6H_4; 65%. ^1H nmr ($CDCl_3$): δ3.14 (3H, d, J_{HP}10Hz, NMe); 3.72 (6H, d, J_{HP}12Hz, OMe); 3.75 (3H, s, ArOMe); 6.44-7.44 (4H, d of d, C_6H_4).

Dimethyl N-methyl-N-(p-chlorophenyl)-phosphoramidate, 1k (Ar = p-Cl-C_6H_4) was synthesised in two steps.

i) N-methyl-p-chloroanilinium chloride (2.45g; 14mmol) was dissolved in $POCl_3$ (4.14g; 27mmol) and refluxed for 4h[139]. Excess $POCl_3$ was removed by evaporation to yield N-methyl-N-(p-chlorophenyl)-phosphoramidodichloridate, $Cl_2P(O)N(Me)C_6H_4$-p-Cl. 99%. ^1H nmr ($CDCl_3$): δ 3.30 (3H, d, J_{HP}14Hz, NMe); 7.50 (4H, m, C_6H_4).

ii) A solution of the dichloridate (3.6g; 14mmol) in MeOH (70ml) was added to a solution of Na (0.65g; 28mmol) in MeOH (50ml). The mixture was refluxed for 1h, then solvent evaporated and the residue redissolved in $CHCl_3$ (50ml). After washing with water (3 x 10ml), solvent was evaporated from the organic phase, yielding 1k .53%. ^1H nmr ($CDCl_3$): δ 3.22 (3H, d, J_{HP}9Hz, NMe); 3.75 (6H, d, J_{HP}12Hz, OMe); 7.33 (4H, m, C_6H_4). Anal. calc.

for $C_9H_{13}ClNO_3P$: C, 43.4; H, 5.2; N, 5.6%.

Found: C, 43.9; H, 5.3; N, 5.8%.

Dimethyl N-methyl-N-(p-trifluoro-methylphenyl)-phosphoramidate, 11 (Ar = p-CF_3-C_6H_4) was synthesised in three steps.

i) p-Trifluoromethylanilinium chloride (5.6g; 28mmol) was dissolved in $POCl_3$ (12.9g; 85mmol) and refluxed for 4h. Excess $POCl_3$ was removed by evaporation and yellow crystals of N-(p-trifluoromethylphenyl)-phosphoramidodichloridate obtained. 89%. mp 90-92°C. ^1H nmr ($CDCl_3$); δ 7.30 (2H, d, J_{HP}8Hz, 2,6-H); 7.53 (2H, d, J_{HH}8Hz, 3,5-H). Anal. calc. for $C_7H_5Cl_2F_3NOP$: C, 30.2; H, 1.8; N, 5.0%. Found: C, 30.7; H, 2.9; N, 5.1%.

ii) The dichloridate (7.0g; 25mmol) was dissolved in MeOH (130ml) and added to a solution of Na (1.3g; 58mmol) in MeOH (90ml), and the solution refluxed for 2h. After removal of solvent the residue was redissolved in $CHCl_3$ (90ml) and washed with water (3 x 25ml). The aqueous phase was extracted with $CHCl_3$ (30ml), and the combined organic portions evaporated to yield dimethyl N-(p-trifluoromethylphenyl)-phosphoramidate, $(MeO)_2P(O)NHC_6H_4$-p-CF_3. 79%. mp 95-97°C. ^1H nmr ($CDCl_3$): δ 3.79 (6H, d, J_{HP}11.6Hz, OMe); 7.08 (2H, d, J_{HH}8.7Hz, 2,6-H); 7.51 (2H, d, J_{HH}8.7Hz, 3,5-H). Anal. calc. for $C_9H_{11}F_3NO_3P$: C, 40.1; H, 4.1; N, 5.2%.

Found: C, 40.2; H, 3.8; N, 5.3%.

iii) The phosphoramidate (4.0g; 15mmol) was dissolved in THF (50ml) and added to a suspension of NaH (0.865g, 80% w/w in oil; 29 mmol) in THF (20ml). After cessation of H_2 evolution, Me_2SO_4 (1.9g; 15mmol) in THF (20ml) was added, and the mixture stirred overnight. After filtering off solids and removing solvent, the residue was redissolved in $CHCl_3$ (80ml) and washed with water (3 x 20ml). The organic portion yielded 11 as an oil. 73%. ^1H nmr ($CDCl_3$): δ 3.25 (3H, d, J_{HP}8.5Hz, NMe); 3.74 (6H, d, J_{HP}11.6Hz, OMe); 7.33 (2H, d, J_{HH}10.5Hz, 2,6-H); 7.57(2H, d, J_{HH}10.5Hz, 3,5-H). Anal. calc. for $C_{10}H_{13}F_3NO_3P$: C, 42.4; H, 4.6; N, 4.9%. Found: C, 42.3; H, 4.2; N, 5.0%.

Tetramethylammonium methyl N-methyl-N-arylphosphoramidates, $NMe_4^{+}\,^{-}O_2P(OMe)NMeAr$, 2i-l were synthesised in the same way as 2a-d.

2i Ar = Ph; 42% ^1H nmr (D_2O): δ 3.03 (3H, d, J_{HP}9Hz, NMe); 3.20 (12H, s, NMe_4^+); 3.53 (3H, d, J_{HP}11Hz, OMe); 7.00-7.50 (5H, m, Ph). Anal. calc. for $C_{12}H_{23}N_2O_3P \cdot 0.5\ H_2O$: C, 50.9; H, 8.5; N, 9.9%.Found: C, 50.75; H, 8.35; N, 10.15%.

2j Ar = p-MeO-C_6H_4; 40%. ^1H nmr (D_2O): δ 3.03 (3H, d, J_{HP}9Hz, NMe); 3.20 (12H, s, NMe_4^{+-}); 3.55 (3H, d, J_{HP}11Hz, OMe); 3.85 (3H, s, ArOMe); 6.90-7.55 (4H, m, C_6H_4). Anal. calc. for $C_{13}H_{25}N_2O_4P \cdot 2H_2O$: C, 45.85; H, 8.5; N, 8.2% . Found: C, 45.85; H, 8.9; N, 8.7%.

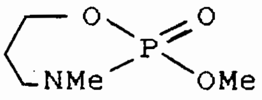
2k Ar = p-Cl-C_6H_4; 75%. ^{1}H nmr (D_2O):

δ 3.02 (3H, d, J_{HP}9Hz, NMe); 3.22 (12H, s, NMe_4^+); 3.50 (3H, d, J_{HP}11Hz, OMe); 7.12-7.40 (4H, m, C_6H_4). Anal. calc. for $C_{12}H_{22}ClN_2O_3P$: C, 46.75; H, 7.1; N, 9.1% Found: C, 46.5; H, 7.15; N, 9.1%.

2l Ar = p-CF_3-C_6H_4; 99%. ^{1}H nmr (D_2O):

δ 3.18 (12H, s, NMe_4^+); 3.19 (3H, d, J_{HP}7.9Hz, NMe); 3.49 (3H, d, J_{HP}11.3Hz, OMe); 7.40 (2H, d, J_{HH}8Hz, 2,6-H); 7.65 (2H, d, J_{HH}8Hz, 3,5-H). Anal. calc. for $C_{13}H_{22}F_3N_2O_3P$: C, 45.6; H, 6.4; N, 8.2%. Found: C, 45.7; H, 6.3; N, 8.0%.

N-methyl-2-methoxy-2-oxo-1,3,2-oxazaphosphorinane,

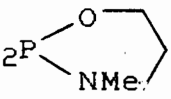


, 40 was synthesised in 2 steps.

i) A solution of 63 (8.3g; 56mmol) in CH_2Cl_2 (10ml) was added to a cooled, stirred solution of 3-aminopropanol (4.2g; 56mmol) and Et_3N (11.3g; 0.112mol) in CH_2Cl_2 (100ml). After 6h stirring at 0°C, the mixture was left overnight, then filtered and the filtrate washed with water (2 x 15ml). The aqueous portions were extracted with CH_2Cl_2 (10ml) and organic portions combined and evaporated. The residue was redissolved in CCl_4 (2ml) and precipitated solids removed. After removal of solvent, 2-methoxy-2-oxo-1,3,2-oxazaphosphorinane was obtained. 24%.

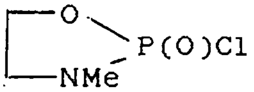
^1H nmr ($CDCl_3$): δ 1.55-2.15 (2H, m, CH_2); 3.10-3.50 (2H, m, NCH_2); 3.70 (3H, d, J_{HP}12.5Hz, OMe); 3.93 (1H, 6s, NH); 4.20-4.50 (2H, m, OCH_2). Anal. calc. for $C_4H_{10}NO_3P.0.1C_6H_{16}ClN$: C, 33.52; H, 7.04; N, 9.35%. Found: C, 33.40; H, 7.05; N, 9.05%.

ii) 2-methoxy-2-oxo-1,3,2-oxazaphosphorinane (2.0g; 13mmol) in THF (20ml) was added to a suspension of NaH (0.68g, 50% w/w in oil, 14mmol) in THF (20ml). After 1h stirring, evolution of H_2 had stopped, and Me_2SO_4 (1.65g; 13mmol) in THF (10ml) was added. The mixture was stirred for 3h, and left standing for a further hour. After filtration and removal of solvent the residue was purified by column chromatography, using 4:1 $CH_3Cl:Et_3N$ as eluant. 40 was obtained in 31% yield. ^1H nmr ($CDCl_3$): δ 1.60-2.30 (2H, m, CH_2); 2.68 (3H, d, J_{HP}12Hz, NMe); 2.90-3.20 (2H, m, NCH_2); 3.68 (3H, d, J_{HP}12.5Hz, OMe). 4.10-4.40 (2H, m, OCH_2). Anal. calc. for $C_5H_{12}NO_3P$: C, 36.37; H, 7.32; N, 8.48%. Found: C, 36.60; H, 7.35; N, 8.40%.

Tetramethylammonium salt of 40, $NMe_4^{+}\,{}^{-}O_2P$ 

The salt was prepared in the same way as salts 2. 69%. ^1H nmr (D_2O): δ 1.70-1.90 (2H, m, CH_2); 2.47 (3H, d, J_{HP}12.6Hz, NMe);2.85-3.05 (2H, m, NCH_2); 3.20 (12H, s, NMe_4^+); 4.15 (2H, d of t, J_{HP}12.7Hz, J_{HH}6.2Hz, OCH_2).

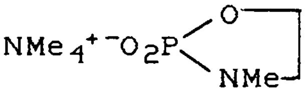
N-methyl-2-chloro-2-oxo-1,3,2-oxazaphospholidin



42

$POCl_3$ (16.4g; 0.11mol) in dioxane (30ml) was added slowly to 2-(methylamino)-ethanol (8.1g; 0.11mol) and Et_3N (21.7g; 0.215mol) in dioxane (150ml) and stirred for 1h[103]. The mixture was filtered and solvent removed from the combined filtrates. Attempts to remove contaminating Et_3NHCl were unsuccessful, and the product decomposed on distillation.

Tetramethylammonium salt of 42,



N-methyl-2-methoxy-2-oxo-1,3,2-oxaza-phospholidin (0.25g; 1.6mmol) was dissolved in MeCN (8ml) and Me_3N added (5ml, as 3.4M solution in MeCN). The mixture was sealed in a glass tube and heated at 60°C for 48h. Evaporation of solvent yielded a small amount of salt insufficient for identification or further reaction, and other products arising from ring-opening reactions.

Acyl methyl N,N-disubstituted phosphoramidates, $MeO(NRR^1)P(O)OC(O)R^2$, 6

Acyl chloride, R^2COCl, in MeCN (15-20ml) was added to the relevant tetramethylammonium phosphate, $NMe_4{}^{+}\,{}^{-}O_2P(NRR^1)OMe$ (1.3 mol-equivalents) in MeCN (20-40ml) and the mixture stirred for 3h at room temperature.

After removal of solids and evaporation of solvent, the residue was redissolved in a minimum volume of CCl_4; precipitated solids were removed by filtering through cotton wool. On evaporation, **6** was obtained, usually as an oil.

6a, benzoyl methyl N,N-dimethylphosphoramidate, R = R^1 = Me; R^2 = Ph; 72%. ^1H nmr ($CDCl_3$): δ 2.80 (6H, d, J_{HP}11Hz, NMe_2); 3.90 (3H, d, J_{HP}12Hz, OMe); 7.45 (3H, m, 3,4,5-H); 8.10 (2H, m, 2,6-H). Anal. calc. for $C_{10}H_{14}NO_4P$: C, 49.4; H, 5.8; N, 5.8%. Found: C, 49.05; H, 5.6; N, 5.7%.

6f, p-methoxybenzoyl methyl N,N-dimethylphosphoramidate, R = R^1 = Me; R^2 = p-MeO-C_6H_4; 85%. ^1H nmr ($CDCl_3$): δ 2.75 (6H, d, J_{HP}11Hz, NMe_2); 3.85 (3H, s, ArOMe); 3.88 (3H, d, J_{HP}11Hz, OMe); 6.95 (2H, d of d, J_{HH}10Hz, 3,5-H); 8.05 (2H, d of d, J_{HH}10Hz, 2,6-H). Anal. calc. for $C_{11}H_{16}NO_5P$: C, 48.4; H, 5.9; N, 5.1%. Found: C, 47.75; H, 6.2; N, 5.05%.

6g, p-chlorobenzoyl methyl N,N-dimethyl phosphoramidate, R=R^1=Me; R^2=p-Cl-C_6H_4; 80%. ^1H nmr ($CDCl_3$): δ2.78 (6H, d, J_{HP}11Hz, NMe_2); 3.85 (3H, d, J_{HP}12Hz, OMe); 7.35 (2H, d, J_{HH}10Hz, 3,5-H); 8.00 (2H, d, J_{HH}10Hz, 2,6-H). Anal. calc. for $C_{10}H_{13}ClNO_4P$: C, 43.2; H, 4.7; N, 5.0%. Found: C, 43.2; H, 4.85; N, 5.2%.

6h, p-nitrobenzoyl methyl N,N-dimethylphosphoramidate, R = R^1 = Me; R^2 = p-NO_2-C_6H_4; ^1H nmr ($CDCl_3$): δ 2.80 (6H, d, J_{HP}11Hz, NMe_2); 3.92 (3H, d, J_{HP}12Hz, OMe);

8.33 (4H, m, C_6H_4). Anal. calc. for $C_{10}H_{13}N_2O_6P$: C, 41.7; H, 4.5; N, 9.8%. Found: C, 41.8; H, 4.8; N, 9.8%.

6i, benzoyl methyl N-methyl-N-phenyl-phosphoramidate, R = Me; R^1 = R^2 = Ph; 52%. ^{1}H nmr ($CDCl_3$): δ 3.33 (3H, d, J_{HP}10Hz, NMe); 3.91 (3H, d, J_{HP}12Hz, OMe); 7.00-8.30 (10H, m, 2 x Ph). Anal. calc. for $C_{15}H_{16}NO_4P$: C, 59.0; H, 5.2; N, 4.6%. Found: C, 58.8; H, 5.35; N, 4.65%.

6j, benzoyl methyl N-methyl-N-(p-methyloxyphenyl)-phosphoramidate, R = Me; R^1 = p-MeO-C_6H_4, R^2 = Ph; 84%. ^{1}H nmr ($CdCl_3$): 3.22 (3H, d, J_{HP}10Hz, NMe); 3.73 (3H, s, ArOMe); 3.88 (3H, d, J_{HP}12Hz, OMe); 6.60-8.12 (9H, m, ArH). Anal. calc. for $C_{16}H_{18}NO_5P$: C, 57.3; H, 5.4; N, 4.2%. Found: C, 57.0; H, 5.4; N, 4.2%.

6k, benzoyl methyl N-methyl-N-(p-chlorophenyl)-phosphoramidate, R = Me; R^1 = p-Cl-C_6H_4; R^2 = Ph; 61%. ^{1}H nmr ($CDCl_3$): δ 3.30 (3H, d, J_{HP}10Hz, NMe); 3.98 (3H, d, J_{HP}12Hz, OMe); 7.10-8.30 (9H, m, ArH). Anal. calc. for $C_{15}H_{15}ClNO_4P$: C, 53.1; H, 4.4; N, 4.1%. Found: C, 52.45; H, 4.55; N, 4.15%.

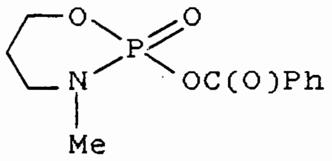
6l, benzoyl methyl N-methyl-N-(p-trifluoromethylphenyl)-phosphoramidate, R = Me, R^1 = p-CF_3-C_6H_4; R^2 = Ph; 73%. ^{1}H nmr ($CDCl_3$): δ 3.37 (3H, d, J_{HP}9.6Hz, NMe); 3.96 (3H, d, J_{HP}11.6Hz, OMe); 8.00-9.53 (9H, m, ArH). Anal. calc. for $C_{16}H_{15}F_3NO_4P$: C, 51.5; H, 4.0; N, 3.75%.

Found: C, 45.25; H, 5.01; N, 4.51%. (Poor microanalysis probably related to trace amounts of $NMe^{+}Cl^{-}$ in sample, which do not affect transfer reaction).

Other mixed anhydrides were made similarly from the relevant salt and acid chloride:

49, benzoyl N,N,N',N'-tetramethylphosphorodiamidate, $(Me_2N)_2P(O)OC(O)Ph$; 83%. ^1H nmr ($CDCl_3$): δ 2.85 (12H, d, J_{HP}11Hz, NMe_2); 7.60 (3H, m, 3,4,5-H); 8.20 (2H, m, 2,6-H).

39, N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane,



; 81%. ^1H nmr ($CDCl_3$): δ 1.70-2.40 (2H, m, CH_2); 2.90 (3H, d, H_{HP}12.5Hz, NMe); 2.95-3.45 (2H, m, NH_2); 4.10-4.60 (2H, m, OCH_2); 7.50 (2H, t, J_{HH}5Hz, 3,5-H); 7.65 (1H, t, J_{HH}5Hz, 4-H); 8.12 (2H, d, J_{HH}5Hz, 2,6-H). Anal. calc. for $C_{10}H_{14}NO_4P$: C, 51.76; H, 5.80; N, 5.76%. Found: C, 50.80; H, 5.50; N, 5.75%.

59b, benzoyl dimethylphosphate, $(MeO)_2P(O)OC(O)Ph$; 97%. ^1H nmr ($CDCl_3$): δ 3.95 (6H, d, J_{HP}12Hz, OMe); 7.45 (3H, m, 3,4,5-H); 8.10 (2H, m, 2,6-H). Anal. calc. for $C_9H_{11}O_5P$: C, 47.0; H, 4.8%. Found: C, 45.8; H, 4.75%.

59a, acetyl dimethylphosphate, $(MeO)_2P(O)OC(O)Me$; 22%.

(i) ^1H nmr ($CDCl_3$): δ 2.27 (3H, d, J_{HP}2Hz, Me); 4.00 (6H, d, J_{HP}12Hz, OMe). ^{31}P nmr ($CDCl_3$): δ-5.32. Anal. calc. for $C_4H_9O_5P$: C, 28.6; H, 5.4%. Found: C, 28.3; H, 5.9%.

(ii) $^{127}(MeO)_3P(O)$ (7.7g; 55mmol), MeCOCl (2.8g; 35mmol) and 3 drops of Et_3N were heated under reflux for 22h. The product mixture was then distilled. bp 50-53°C/1mm. The distilled product was contaminated with $(MeO)_3P(O)$.

6m, trifluoracetyl methyl N,N-dimethylphosphoramidate, $R=R^1=Me$; $R^2=CF_3$, was synthesised by addition of $(CF_3CO)_2O$ (2.6μl; 0.02mmol) to a suspension of 2a (3.9mg; 0.02mmol) in CD_3CN (0.6ml) and reacted *in situ* (Chapter 6, 6.1.1). ^1H nmr (CD_3CN): δ2.75 (6H, d, J_{HP}10.8Hz, NMe_2); 3.85 (3H, d, H_{HP}11.8Hz, OMe).

Methyl N, N-dimethylphosphoramidochloridate, $MeO(Me_2N)P(O)Cl$, 56.

(i) 63 (6.8g; 50mmol) was added to a solution of Me_2NH (4.2g; 90mmol) in ether (50ml) with cooling (-30°C), and stirred for 1h. After warming to room temperature, the reaction mixture was filtered and solvent removed under reduced pressure yielding 56, but contaminated with $Me_2NH_2^+Cl^-$.

(ii) A solution of Me_2NH (35ml, 0.327M in ether; 11 mmol) and Et_3N (1.2g; 12mmol) in ether was added to a cooled (-30°C) solution of <u>63</u> (1.8g; 12mmol) in ether (25ml). After 2.5h, the mixture was allowed to warm to room temperature, solids were filtered off and solvent removed from the filtrate. The yellow liquid obtained was distilled to yield <u>56</u>. 17.5%. ^1H nmr ($CDCl_3$): δ2.66 (6H, d, J_{HP}13.6Hz, NMe_2); 3.79 (3H, d, J_{HP}13.4Hz, OMe).

N,N-dimethylcarboxyamides, $RCONMe_2$, <u>4</u>.

<u>4a, N,N-dimethylbenzamide, R = Ph,</u> was prepared[42] by adding PhCOCl (9.8g; 70mmol) to a cooled solution of $NMe_2H.HCl$ (5.0g; 60mmol) in 8% aq. NaOH solution (95ml). After 0.5h, the mixture was extracted with benzene (3 x 30ml) and solvent removed from the organic portion, yielding white, crystalline product. 85%, mp 40-42°C. ^1H nmr ($CDCl_3$): δ 3.0 (6H, bs, NMe_2); 7.3 (5H, s, Ph). Anal. calc. for $C_9H_{11}NO$: C, 72.5; H, 7.4; N, 9.4%. Found: C, 72.6; H, 7.4; N, 9.4%.

<u>4m, N-N-dimethyltrifluoroacetamide, R = CF_3,</u> was synthesised[42] by the dropwise addition of $(CF_3CO)_2O$ (15g; 7.1mmol) in CH_2Cl_2 (20ml) to a cold, saturated solution of Me_2NH in CH_2Cl_2 (50ml). After 3h stirring, the reaction mixture was washed with 5% aq. $NaHCO_3$ solution (3 x 15ml), and solvent removed from the organic portion. 22%. ^1H nmr ($CDCl_3$). δ 3.06 (3H, d, J_{HF}0.68Hz, NMe); 3.15 (3H, q, J_{HF}1.48Hz, NMe).

Pyrophosphates, $[MeO(R)PO]_2O$.

58, dimethyl N,N,N'N'-tetramethyl-pyrophosphorodiamidate, R = NMe_2. A solution of 56 (0.7g; 4.5mmol; made by (ii)) in ether (15ml) was added over 0.5h to a cooled suspension of 2a (1.1g; 5.1mmol) in ether (15ml). Reaction was continued for 1h at 0°C and 2h at room temperature, then solids were filtered and solvent removed from the filtrate. 53%. ^1H nmr ($CDCl_3$): δ 2.70 (12H, d, J_{HP}13.7Hz, NMe); 3.83 (6H, d, J_{HP}13.4Hz, MeO).

61, tetramethylpyrophosphate, R=OMe. 64 (3.65g; 25mmol) and $(MeO)_3P(O)$ (17.5g; 0.125ml) were heated at 150°C for 2h, and the mixture then fractionally distilled so as to remove excess $(MeO)_3P(O)$. 63%. bp 128°C/1mm. ^1H nmr ($CDCl_3$): δ 3.77 (d, J_{HP}11Hz, MeO). ^{31}P nmr ($CDCl_3$): δ -9.82. Anal. calc. for $C_4H_{12}O_7P$: C, 20.5; H, 5.1%. Found: C, 20.45; H, 5.7%.

Dimethylphosphoric acid, $(MeO)_2$ P(O)OH, 62 was synthesised by the addition of water (0.15g; 8.3mmol) to 64 (0.6g; 5mmol), and stirring for 18h. 38%. ^1H nmr ($CDCl_3$): δ 3.73 (6H, d, J_{HP}11Hz, OMe); 11.12 (1H, s, OH). ^{31}P nmr ($CDCl_3$): δ 3.25 Anal. calc. for $C_2H_7O_4P.H_2O$: C, 16.7; H, 6.3%. Found: C, 16.5; H, 5.7%.

3) REACTIONS

Reaction between tetramethylammonium phosphates 2 and acyl chlorides.

Acyl chloride, R^2COCl (R^2 = Me, Ph; 1mol-equivalent) was added to a suspension of 2 in MeCN (10-15ml), and the mixture refluxed for 4h. After cooling, solids were removed by filtration, washed with MeCN, and solvent removed from the combined filtrates. The residue was examined by ^1H nmr, and each time indicated formation of only carboxyamide, $R^2C(O)NRR^1$, which was identified by comparison with literature nmr data[38].

Rate measurements.

In a typical experiment, mixed anhydride 6 (20μl) was dissolved in deuterated solvent (0.4ml) in an nmr tube, the tube was sealed and then incubated in a thermostatted waterbath at the required temperature (0.5°C). Progress of reaction was monitored by ^1H nmr, using the ratio of the N-methyl signal integrals from substrate and product (Chapter 2, 2.3) to calculate the percentage of product present at any time, and then inserting these values into the first-order rate law. Reactions were followed to *ca* 70% completion, and gave linear plots with $r > 0.990$. As far as possible, the same substrate batch and solvent bottle were used in comparative studies, and such experiments were carried out simultaneously.

Reaction of methyl N,N-dimethylphosphoramidochloridate 56 with benzoic acid[127].

56 (2.0g; 13mmol, made by (i)) was dissolved in 3:1 MeCN:ether (40ml) and added dropwise to a solution of Et_3N (0.6g; 6mmol), DMF (10.7g; 10mmol) and PhCOOH (1.3g; 10mmol) in MeCN (30ml). After 1h reflux, ether (50ml) was added to the solution, and solids removed by filtration. The filtrate was evaporated down under reduced pressure and the residue redissolved in $CHCl_3$ (3.5ml) and washed with water (3 x 20ml). Solvent was removed from the organic portion to give a mixture of $PhCONMe_2$ (58%), $MeOP(O)(NMe_2)_2$ (9%) and PhCOOH (33%), as determined by g.c. analysis.

Trapping of monomeric methylmetaphosphate, $MeOPO_2$[151].

6a (20ml) and PhNHMe (22ml) were dissolved in CD_3CN (0.4ml), the solution sealed in an nmr tube, and the tube incubated at 50°C. After 60h, the mixture was removed from the tube, and solvent and excess amine removed by evaporation. The residue was identified by ^1H nmr as a mixture of $PhCONMe_2$ and the N-methylanilinium salt of methyl N-methyl-N-phenylphosphoramidic acid. ^1H nmr ($CDCl_3$): δ 2.90 (3H, s, NMe^+); 3.20 (3H, d, J_{HP}9Hz, NMe); 3.70 (3H, d, J_{HP}11Hz, OMe); 6.7 (2H, bs, NH_2^+); 7.20 (10H, m, 2 x Ph).

APPENDICES

Appendix 1: Calculated and Observed Structure Factors, and Analysis of Variance for 39, N-methyl-2-benzoyloxy-2-oxo-1,3,2-oxazaphosphorinane.

Structure Factors

H	k	L	Fu	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC	H	K	L	FO	FC
2	0	0	10	10	11	2	0	28	29	23	4	0	6	5	5	8	0	6	6	1	2	1	40	40
4	0	0	33	33	12	2	0	34	34	1	5	0	5	6	6	8	0	4	4	2	2	1	32	31
6	0	0	88	90	13	2	0	18	18	2	5	0	6	5	7	8	0	5	5	3	2	1	36	35
8	0	0	11	11	14	2	0	26	26	3	5	0	9	10	8	8	0	3	3	4	2	1	20	19
10	0	0	9	10	15	2	0	11	11	4	5	0	8	8	9	8	0	4	4	5	2	1	8	8
12	0	0	21	21	16	2	0	6	6	5	5	0	18	17	10	8	0	3	4	6	2	1	26	26
14	0	0	2	1	17	2	0	25	25	6	5	0	8	7	11	8	0	3	4	7	2	1	23	23
16	0	0	51	52	19	2	0	6	7	7	5	0	14	13	12	8	0	4	4	8	2	1	58	56
18	0	0	28	29	20	2	0	9	9	8	5	0	19	19	2	0	1	74	79	9	2	1	54	53
20	0	0	19	20	21	2	0	11	12	9	5	0	2	3	4	0	1	86	91	10	2	1	19	19
22	0	0	12	11	23	2	0	5	5	10	5	0	6	6	6	0	1	33	33	11	2	1	14	13
24	0	0	9	9	25	2	0	6	6	11	5	0	11	11	8	0	1	58	61	12	2	1	15	14
26	0	0	3	2	1	3	0	9	9	12	5	0	22	22	10	0	1	12	11	13	2	1	9	9
1	1	0	26	26	2	3	0	38	37	13	5	0	23	23	12	0	1	2	3	14	2	1	10	10
2	1	0	65	67	4	3	0	2	2	14	5	0	3	2	14	0	1	27	27	15	2	1	26	26
3	1	0	105	109	5	3	0	27	27	15	5	0	11	12	16	0	1	5	5	16	2	1	6	6
4	1	0	51	54	6	3	0	6	6	16	5	0	4	3	18	0	1	32	32	17	2	1	16	16
5	1	0	44	44	8	3	0	72	70	19	5	0	14	13	20	0	1	7	8	18	2	1	20	21
6	1	0	63	63	9	3	0	3	3	20	5	0	4	5	22	0	1	10	10	19	2	1	12	12
7	1	0	46	45	10	3	0	16	17	1	6	0	17	18	24	0	1	13	12	20	2	1	7	8
8	1	0	15	14	11	3	0	10	10	2	6	0	6	6	26	0	1	10	9	21	2	1	3	3
9	1	0	91	90	12	3	0	26	25	3	6	0	3	2	0	1	1	110	111	23	2	1	6	6
10	1	0	14	14	13	3	0	16	16	4	6	0	18	19	1	1	1	60	61	24	2	1	4	3
11	1	0	20	20	14	3	0	17	18	5	6	0	24	25	2	1	1	25	26	25	2	1	10	9
12	1	0	7	6	19	3	0	5	5	6	6	0	13	15	3	1	1	70	71	0	3	1	35	34
13	1	0	22	22	20	3	0	4	4	7	6	0	3	3	4	1	1	39	39	1	3	1	14	14
14	1	0	23	24	21	3	0	7	7	8	6	0	6	7	5	1	1	17	17	2	3	1	15	15
15	1	0	34	35	24	3	0	6	6	11	6	0	10	10	6	1	1	31	31	3	3	1	29	28
16	1	0	5	5	0	4	0	24	24	12	6	0	3	3	7	1	1	35	35	4	3	1	16	17
17	1	0	9	9	1	4	0	13	14	15	6	0	8	8	8	1	1	18	18	5	3	1	22	22
18	1	0	36	37	2	4	0	20	20	16	6	0	2	2	9	1	1	34	34	6	3	1	42	42
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2	[illegible]	[illegible]	[illegible]	[illegible]	10	2	5	8	8	6	5	5	6	5	15	1	6	12	11	11	4	6	3	3
3	7	4	6	5	11	2	5	4	4	7	5	5	5	6	16	1	6	3	3	12	4	6	6	6
4	7	4	5	5	13	2	5	17	17	8	5	5	5	5	17	1	6	3	2	13	4	6	4	3
6	7	4	5	5	14	2	5	6	6	9	5	5	4	4	18	1	6	4	5	14	4	6	5	5
7	7	4	6	6	15	2	5	11	11	10	5	5	10	10	0	2	6	17	16	2	5	6	3	3
8	7	4	7	7	16	2	5	5	5	11	5	5	10	10	1	2	6	20	19	3	5	6	5	5
9	7	4	4	5	18	2	5	8	8	14	5	5	3	3	2	2	6	7	7	4	5	6	5	5
10	7	4	6	6	19	2	5	10	11	15	5	5	5	5	3	2	6	3	3	5	5	6	3	3
11	7	4	4	4	0	3	5	30	30	1	6	5	3	3	4	2	6	5	5	6	5	6	4	3
2	0	5	48	49	1	3	5	8	7	2	6	5	6	6	5	2	6	11	11	7	5	6	5	5

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
8	5	6	5	4	0	1	7	3	3	6	2	7	4	4	11	3	7	6	6	8	0	8	3	2
9	5	6	9	9	1	1	7	7	7	7	2	7	8	9	1	4	7	6	6	1	1	8	4	4
11	5	6	5	5	3	1	7	5	4	8	2	7	3	3	2	4	7	10	10	4	1	8	7	7
0	6	6	6	6	4	1	7	8	9	9	2	7	5	5	3	4	7	3	3	5	1	8	6	6
1	6	6	7	6	5	1	7	9	9	10	2	7	3	2	4	4	7	6	6	7	1	8	5	5
2	6	6	4	4	6	1	7	4	3	12	2	7	3	3	5	4	7	5	5	8	1	8	4	4
3	6	6	5	5	8	1	7	4	4	13	2	7	10	10	8	4	7	9	9	1	2	8	7	7
4	6	6	4	3	10	1	7	9	10	14	2	7	3	3	9	4	7	3	3	2	2	8	2	2
5	6	6	8	7	11	1	7	4	4	0	3	7	10	11	0	5	7	9	8	4	2	8	3	3
2	0	7	10	10	12	1	7	3	3	1	3	7	7	7	1	5	7	5	4	5	2	8	6	6
4	0	7	9	10	13	1	7	2	3	2	3	7	4	5	2	5	7	4	3	6	2	8	2	3
6	0	7	5	5	14	1	7	6	6	3	3	7	3	2	4	5	7	7	6	7	2	8	4	4
8	0	7	19	19	1	2	7	3	3	4	3	7	4	4	0	0	8	8	7	1	3	8	5	5
10	0	7	4	5	2	2	7	4	4	5	3	7	11	11	2	0	8	7	7	2	3	8	8	5
12	0	7	8	9	3	2	7	6	7	6	3	7	6	6	4	0	8	10	11	3	3	8	6	6
14	0	7	7	7	5	2	7	4	4															

Analysis of Variance

```
                GGG    UGG    GUG    UUG    GGU    UGU    GUU    UUU    ALL

     N          173    116    135    135    139     98    126    115   1032

     V           50     40     45     42     51     41     45     44     45


SIN THETA    0.00 -  .19 -  .24 -  .27 -  .30 -  .33 -  .35 -  .37 -  .39 -  .41 -  .43

     N          112    108     91    109    126    101     99    106    113     72

     V           81     54     39     41     40     35     34     34     33     32


SQRT(F/FMAX) 0.00 -  .15 -  .17 -  .20 -  .21 -  .24 -  .26 -  .30 -  .34 -  .40 - 1.00

     N          106    102    148     59    132     86    109    103     92    100

     V           29     32     39     42     47     37     40     44     49     78


   ABS(H)         0      1      2      3      4      5      6      7      8      9     10     11     12     13   REST

     N           31     54     65     51     66     56     62     50     61     48     56     45     49     39    304

     V           69     53     63     52     54     45     44     40     51     42     41     41     46     31     36


   ABS(K)         0      1      2      3      4      5      6      7      8      9     10     11     12     13   REST

     N           94    178    166    149    140    118     95     66     31      0      0      0      0      0      0

     V           66     51     46     42     38     39     41     37     23      0      0      0      0      0      0


   ABS(L)         0      1      2      3      4      5      6      7      8      9     10     11     12     13   REST

     N          152    167    163    149    136    112     90     50     18      0      0      0      0      0      0

     V           55     54     48     44     34     35     37     38     30      0      0      0      0      0      0
```

Appendix 2: Additional constants used in Molecular Mechanics calculations (Chapter 4; ref 121)

Bond moments (Debye)

O	P	-5.69
O	P	-6.03
N	P	-4.63

Bonding constants (kcalmol^{-1}.)

		$r_o(A^o)$	$1/2k_r$
O	P	1.480	528
O	P	1.610	237
N	P	1.610	237

Bending constants (kcalmol^{-1})

			θ_o (degrees)	$1/2k_\theta$
O	P	O	108.2	98.9
O	P	O	102.6	48.1
O	P	N	102.6	48.1
O	P	N	108.2	98.9
C	N	P	120.5	47.6
C	O	P	120.5	47.6

Torsion constants (kcalmol^{-1})

				V_1	V_2	V_3
X	O	P	X	0	1.50	1.50
X	N	P	X	0	1.50	1.50
X	C	X	P	0	0	1.80
C	C	O	P	0	0.50	0.00
O	C	O	P	-3.285	5.60	0.00

REFERENCES

1. David E. Metzler; **Biochemistry. The Chemical Reactions of Living Cells**, Int. Ed., Academic Press (1979).

2. V.M. Clark, D.W. Hutchinson, A.I. Kirby and S.G. Warren; **Angew. Chem.**, 76, 704 (1964).

3. C. Fest and K-J. Schmidt; **The Chemistry of Organophosphorus Pesticides**, 2nd Ed., Springer-Verlag (1982).

4. D.E.C. Corbridge; **Studies in Inorganic Chemistry. 2. Phosphorus. An Outline of its Chemistry, Biochemistry and Technology**, 2nd Ed., Elsevier (1980).

5. a Theodore F. Hendrickse, Valerie Mizrahi and Tomasz A. Modro, **Phosphorus and Sulphur**, 20, 93 (1984).
   b Valerie Mizrahi; **Ph.D. Thesis** (1983).
   c T.F. Hendrickse; **M.Sc. Thesis** (1983).

6. a Bette Davidowitz and Tomasz A. Modro; **S. Afr. J.Chem.**, 33, 74 (1980).
   b Tomasz A. Modro and Bloys P. Rijkmans; **J. Org. Chem.**, 47, 3208 (1982).

7. a Valerie Mizrahi, Klaus R. Koch and Tomasz A. Modro; **S. Afr. J. Chem.**, 36, 111 (1983).
   b Tomasz A. Modro, Keith Yates and Francoise Beaufays; **Can. J. Chem.**, 55, 3050 (1977).

8. a Paul Haake and Gary W. Allen; **Proc. Nat. Acad. Sci. USA**, 68, 2691 (1971).

b Gary W. Allen and Paul Haake; **J. Am. Chem. Soc.**, 95, 8080 (1973).

9. Daniel E. Koshland, Jr.; **J. Am. Chem. Soc.**, 74, 2286 (1952).

10. David R. Phillips and Thomas H. Fife; **J. Am. Chem. Soc.**, 90, 6803 (1968).

11. Giovanni di Sabato and William P. Jencks; **J. Am. Chem. Soc.**, 83, 4400 (1961).

12. Giovanni Di Sabato and William P. Jencks; **J. Am. Chem. Soc.**, 83 4393 (1961).

13. David R. Phillips and Thomas H. Fife; **J. Org. Chem.**, 34, 2710 (1969).

14. A.G. Jackson, G.W. H.Kenner, G.A. Moore, R. Ramage and W.D. Thorpe; **Tetrahedron Lett.**, 40, 3627 (1976).

15. Ramon Mestres and Claudio Palomo; **Synthesis**, 288 (1982).

16. Ramon Mestres and Claudio Palomo; **Synthesis**, 218 (1981).

17. Hsing-Jang Liu, Wong Hong Chan and Sing Ping Lee; **Tetrahedron Lett.**, 46, 4461 (1978).

18. Satoru Masamune, Susumu Kamata, James Diakur, Yoshikazu Sugihara and Gordon S. Bates; **Can. J. Chem.**, 53, 3693 (1975).

19. John C. Sheehan and Victor S. Frank; **J. Am. Chem. Soc.**, 72, 1312 (1950).

20. George W. Anderson and Richard W. Young; **J. Am. Chem. Soc.**, 74, 5307 (1952).

21. A. Gorecka, M. Leplawy, J. Zabrocki and A. Zwierzak; **Synthesis**, 474 (1978).

22. C.D. Hurd and M.F. Dull; **J. Am. Chem. Soc.**, 54, 3427 (1932).

23. Gerhard W. Fischer and Peter Schneider; **Chem. Ber.**, 106, 435 (1973).

24. K.A. Petrov and A.A. Neimyshema; **J. Gen. Chem. USSR (Eng. Trans.)**, 29, 1793 (1959).

25. Hsing-Jang Liu, Wing Hong Chan and Sing Ping Lee; **Synthetic Commun.**, 9, 31 (1979).

26. Franz Effenberger and Gerd Konig; **Chem. Ber.**, 114, 916 (1981).

27. Erik B. Pedersen, N. Ole Vesterger and Sven-Olov Lawesson; **Synthesis**, 547 (1972).

28. Brian C. Challis and A. David Frenkel; **J. Chem. Soc., Perkin Trans.** 2, 192 (1978).

29. Brian C. Challis, Judith A. Challis and James N. Iley; **J. Chem. Soc., Perkin Trans.** 2, 813 (1978).

30. Brian C. Challis and James N. Iley; **J. Chem. Soc., Perkin Trans.** 2, 699 (1985).

31. a Jill Symes and Tomasz A. Modro; **Can J. Chem.**, 64, 1702 (1986).

b Jillian Symes and Tomasz A. Modro; **Phosphorus and Sulfur**, in press (1988).

32. Barry K. Carpenter; **Determination of Organic Reaction Mechanisms**, Wiley-Interscience (1984).

33. R.A.Y. Jones; **Physical and mechanistic organic chemistry**, 2nd edition, Cambridge University Press (1984).

34. 34. D. Balarev; **Z. Anorg. Allg. Chem**; 88, 145 (1914); *ibid* 99, 191 (1917).

35. G. Kamai and F.M. Kharrasova; **Zh. Obshch. Khim.**, 27, 3064 (1957).

36. K. Sasse; **Organische Phosphorverbindungen, Methoden der Organischen Chemie**, Vol. X11/2, Georg Thieme Verlag, Stuttgart, (1964).

37. F.A. Bovey; **NMR Data Tables for Organic Compounds, Vol. 1**, John Wiley and Sons, Inc. (1967).

38. L.A. La Planche and M.T. Rogers; **J. Am. Chem. Soc.**, 86, 337 (1964).

39. M.B. Robin, F.A. Bovey and H. Basch; **The Chemistry of the Amides**, ed. Jacob Zabicky, Interscience (1970).

40. Keith J. Laidler; **Chemical Kinetics**, 2nd Edition, McGraw-Hill Inc. (1964).

41. K. Ostwald; **Z. Physik. Chem.**, 2, 127 (1888).

42. A. Vogel; **Textbook of Practical Organic Chemistry**, 4th edition, Longman (1978).

43. a W.W. Butcher and F.H. Westheimer; **J. Am. Chem. Soc.**, 77, 2420 (1955).

b C.A. Bunton, D.A. Llewellyn, K.G. Oldham, and C.A. Vernon; **J. Chem. Soc.**, 3574 (1958).

44\. a James B. Conant and Alan A. Cook; **J. Am. Chem. Soc.**, 42, 830 (1920).

b Judith A. Maynard and J.M. Swan; **Aust. J. Chem.**, 16, 596 (1963).

45\. a S. Cocks and T.A. Modro; **Tetrahedron Lett.**, 26, 945 (1985).

46\. Narimasa Iwamoto, Yoshiki Okamoto and Setsuo Takamuku; **Bull. Chem. Soc. Jpn.**, 59, 1505 (1986).

47\. Paul Haake and Gary W. Allen; **Bioorganic Chemistry**, 9, 325 (1980), and references therein.

48\. Patricia S. Traylor and F.H. Westheimer; **J. Am. Chem. Soc.**, 87, 553 (1965).

49\. Martin J.P. Harger and Sally Westlake; **Tetrahedron**, 38, 1511 (1982).

50\. a Leslie M. Loew; **J. Am. Chem. Soc.**, 98, 1630 (1976).

b Leslie M. Loew and William R. MacArthur; *ibid*, 99, 1019 (1977).

51\. Charles H. Clapp and F.H. Westheimer, **J. Am. Chem. Soc.**, 96, 6710 (1974).

52\. Charles H. Clapp, Arnold Satterthwait and F.H. Westheimer; **J. Am. Chem. Soc.**, 97, 6873 (1975).

53. a Arnold C. Satterthwait and F.H. Westheimer; **J. Am. Chem. Soc.**, 102, 4464 (1980).

b Arnold C. Satterthwait and F.H. Westheimer; *ibid*, 103, 1177 (1981).

54. E.M. Kosower; **An Introduction to Physical Organic Chemistry**, Wiley (1968).

55. C. Reichardt; **Solvent Effects in Organic Chemistry**, Verlag Chemie (1978), and references therein.

56. W.N. White and E.F. Wolfarth; **J. Org. Chem.**, 35, 2196 (1970); *ibid*, 3585.

57. N.S. Isaacs and A.A.R. Laila; **J. Chem. Soc., Perkin Trans.** 2, 1470 (1976).

58. A.C. Satterthwait and F.H. Westheimer; **J. Am. Chem. Soc.**, 100, 3197 (1978).

59. a Kim C. Calvo and F.H. Westheimer; **J. Am. Chem. Soc.**, 105, 2827 (1983).

b F. Ramirez, J.F. Maracek and S.S. Yemul; **J. Am. Chem. Soc.**, 104, 1346 (1982).

60. a F. Ramirez and J.F. Maracek; **Tetrahedron**, 35, 1581 (1979).

b See also F.H. Westheimer; **Chem. Rev.**, 81, 313 (1981).

61. C.D. Johnson; **The Hammett Equation**, Cambridge University Press (1973).

62. B.M. Anderson and W.P. Jencks; **J. Am. Chem. Soc.**, 82, 1773 (1960).

63. Brian C. Challis and James N. Iley; **J. Chem. Soc., Perkin Trans.** 2, 1489 (1987).

64. H. van Bekkum, P.E. Verkade and B.M. Wepster; **Rec. Trav. Chem.**,78, 815 (1959).

65. C.D. Schmulbach and Russell S. Drago; **J. Am. Chem. Soc.**, 82, 4484 (1960).

66. Richard L. Middaugh, Russel S. Drago and Robert J. Niedzielski; **J. Am. Chem. Soc.**, 86, 388 (1964).

67. R.C. Carlson and R.S. Drago; **J. Am. Chem. Soc.**, 84, 2320 (1962).

68. D.P.N. Satchell and R.S. Satchell;**Chem Rev.**, 69, 251 (1969).

69. Peter Sykes; **A guidebook to mechanism in organic chemistry**, 4th edition, Longman (1980).

70. J.A. Pople and D.C. Beveridge; **Approximate Molecular Orbital Theory**, McGraw-Hill Inc. (1970).

71. Daniel G. McCarthy and Anthony F. Hegarty; **J.Chem. Soc., Perkin Trans. 2**, 1085 (1977).

72. Henry S. Rzepa; **Tetrahedron**, 37, 3107 (1981).

73. Steve A. Glover, Valerie Mizrahi and Tomasz A. Modro; **J. Chem. Soc., Perkin Trans. 2**, 325 (1984).

74. Jean-Marie Lehn, Georges Wipff and Hans-Beat Burgi; **Helvetica Chemica Acta**, 57, Fasc. 2, 493 (1974).

75. J.C. Bollinger, R. Houriet, C.W. Kern, D. Perret, J. Weber and T. Yvernault; **J. Am. Chem. Soc.**, 107, 5352 (1985).

76. Tomasz A. Modro, Henry S. Rzepa and Jill Symes; **J. Chem. Soc., Perkin Trans. 2**, 767 (1987).

77. M.J.S. Dewar, M.L. McKee and H.S. Rzepa; **J. Am. Chem. Soc.**, 100, 3607 (1978).

78. H. S. Rzepa, **J. Chem. Soc., Chem. Commun.**, 939 (1981).

79. M.J.S. Dewar and A.B. Pierini; **J. Am. Chem. Soc.**, 106, 203 (1984).

80. M.J.S. Dewar, S. Olivella and H.S. Rzepa; **J. Am. Chem. Soc.**, 100, 5650 (1978).

81. P. Deslongchamps; **Stereoelectronic effects in Organic Chemistry**, Pergamon Press (1983).

82. a Andrew J. Briggs, Robert Glenn, Peter G. Jones, Anthony J. Kirby and P. Ramaswamy; **J. Am. Chem. Soc.**, 106, 6200 (1984).

b Peter G. Jones and Anthony J. Kirby; *ibid*, 6207.

83. David G. Gorenstein, Bruce A. Luxon and John B. Findlay; **J. Am. Chem. Soc.**, 101, 5869 (1979).

84. Peter G. Perkins and James J.P. Stewart; **J. Chem. Soc., Faraday Trans.** 2, 78, 285 (1982).

85. J. Symes, T.A. Modro and M.L. Niven; **Phosphorus and Sulphur**, 36, 171 (1988).

86. a Dorota A. Adamaik, Ryszard Kinas, Wolfram Saeger and Wojciech J. Stec; **Angew. Chem. Int. Ed. Engl.**, 16, 330 (1977).

b S. Garcia-Blanco and A. Perales; **Acta Cryst.**, B28, 2647 (1972).

87. Isabella L. Karle, Jean M. Karle, William Egan, Gerald Zon and Joan A. Brandt; **J. Am. Chem. Soc.**, 99, 4803 (1977).

88\. a Dorota A. Adamaik, Maria Gdaniec, Krysztof Pankiewicz and Wojciech J. Stec; **Angew. Chem. Int. Ed. Engl.**, <u>19</u>, 549 (1980).

b A. Perales and S. Garcia-Blanco; **Acta Cryst.**, <u>B33</u>, 1935 (1977).

89\. Arthur Camerman, H. Warren Smith and Norman Camerman; **Acta Cryst.**, <u>B33</u>, 678 (1977).

90\. Norman Camerman and Arthur Camerman; **J. Am. Chem. Soc.**, <u>95</u>, 5038 (1973).

91\. Shirley D. Cutbush, Stephen Neidle, Graham N. Taylor and John L. Gaston; **J. Chem. Soc., Perkin Trans. 2**, 980 (1981).

92\. R.N. Hunston, M. Jehangir, A.S. Jones and R.T. Walker; **Tetrahedron**, <u>36</u>, 2337 (1980).

93\. C. Richard Hall and Thomas D. Inch; **Tetrahedron**, <u>36</u>, 2059 (1980).

94\. Robert O. Hutchins, Bruce E. Maryanoffs, Mario J. Castillo, Karl D. Hargrave and Andrew T. McPhail; **J. Am. Chem. Soc.**, <u>101</u>, 1600 (1979).

95\. Gurdip S. Baywa, Wesley G. Bentrude, N.S. Pantales, M. Gary Newton and J. Howard Hargis; **J. Am. Chem. Soc.**, <u>101</u>, 1603 (1979).

96. David G. Gorenstein, Robert Powell and John Findley; **J. Am. Chem. Soc.**, 102, 5077 (1980).

97. David G. Gorenstein, Debojyoti Kar, Bruce A. Luxon and Robert R. Momii; **J. Am. Chem. Soc.**, 98, 1688 (1976).

98. S. Chandrasekaran and Wesley G. Bentrude; **Tetrahedron Lett.**, 21, 4671 (1980).

99. Robert Pujol, Jean P. Mayard, Jaques Navech and Ferdinand Mathis; **C.R. Acad. Sci., Ser. B**, 274, 66 (1972).

100. Michel Mulliez and Robert Wolf; **Bull. Soc. Chim. Fr.**, 101 (1986).

101. Hansjorg Eibl; **Proc. Natl. Acad. Sci. USA**, 75, 4074 (1978).

102. C. Richard Hall and Thomas D. Inch; **J. Chem. Soc., Perkin Trans. 1**, 1647 (1979).

103. Robert H. Iwamoto, Edward M. Acton, Leon Goodman and B.R. Baker; **J. Org. Chem.**, 26, 4743 (1961).

104. H.B. Burgi, J.D. Dunitz and Eli Shefter; **J. Am. Chem. Soc.**, 95, 5065 (1973).

105. A.C.T. North, D.C. Phillips and F. Scott Mathews; **Acta Cryst.**, A24, 351 (1968).

106. G.M. Sheldricks; SHELX-76, **in Computing in Crystallography**, Eds H. Schenk, R. Oltof-Hazekamp, H. von Koningsveld and G.C. Bassi, Delft University Press, 34 (1978).

107. M. Nardelli; **Comput. Chem.**, 7, 95 (1983).

108. W.D.S. Motherwell; **PLUTO, plotting program** (1974).

109.a D. Cremer and J.A. Pople; **J. Am. Chem. Soc.**, 97, 1354 (1975).

b M. Nardelli; **Acta Cryst.**, C39, 1141 (1983).

110. Janina Karolak-Wojciechowska, Michal Wieczorek, Andrej Zwierzak and Stefan Zawadzki; **J. Chem. Soc., Perkin Trans. 1**, 146 (1979).

111. J. Dunitz; **X-ray Analysis and the Structure of Organic Molecules**, Cornell University Press (1979).

112. James E. Huheey; **Inorganic Chemistry. Principles of Structure and Reactivity**, 2nd edition, Harper and Row (1978).

113. N.C. Allinger; **Calculations of Molecular Structure and Energy by Force-Field Methods**, Advances in Physical Organic Chemistry, Academic Press, 13, (1976).

114.a J.B. Hendrikson; **J. Am. Chem. Soc.**, 83, 4537 (1961); *ibid*, 86, 4854 (1964).

b K.B. Wiberg; **J. Am. Chem. Soc.**, 87, 1070 (1965).

115. E.W. Garbisch Jr.; **J. Am. Chem. Soc.**, 87, 505 (1965).

116. T. Ooi, R.A. Scott, G. Vanderkovic and H.A. Scheraga; **J. Chem. Phys.**, 46, 4410 (1967).

117.a G.L. Casalone, C. Mariani, A. Mugnoli and M. Simonetta; **Acta Cryst.**, 22, 228 (1967).

b G.L. Casalone, C. Mariani, A. Mugnoli and M. Simonetta; **Theoret. Chim. Acta**, 8, 228 (1967).

118. Massimo Simonetta, Giorgio Favini, Carla Mariani and Paolo Gramaccione; **J. Am. Chem. Soc.**, 90, 1280 (1968).

119. J. Dillen; **Chemistry Department**, Pretoria University.

120. N.L. Allinger and Y.H. Yuh; **Q.C.P.E.**, 395 (1980).

121. S.J. Weiner, P.A. Kollman, D.T. Nguyen and D.A. Case; **J. Comp. Chem.**, 7, 230 (1986).

122.a J. Emsley and D. Hall; **The Chemistry of Phosphorus**, Harper and Row (1976).

b Inci Oney and Michael Caplow; **J. Am. Chem. Soc.**, 89, 6972 (1967).

123 Bette Davidowitz and Tomasz A. Modro; **J. Chem. Soc., Perkin Trans. 2**, 303 (1985).

124. Edgar Niecke and Wilhelm Flick; **Angew. Chem. internat. Edit.**, 13, 134 (1974).

125. Soon Ng; **J. Chem. Soc. (A)**, 1586 (1971).

126. A. Arietta, T. Garcia, J.M. Lago and C. Palomo; **Synthetic Commun.**, 13, 471 (1983).

127. Friedrich Cramer and Manfred Winter; **Chem. Ber.**, 94, 989 (1961).

128.a A.D.F. Toy; **J. Am. Chem. Soc.**, 70, 3882 (1948).

b A.D.F. Toy; **J. Am. Chem. Soc.**, 71, 2268 (1949).

129. R.J. W. Cremlyn, B.B. Dewhurst and D.H. Wakeford; **J. Chem. Soc. (C)**, 2028 (1971).

130. A.D.F. Toy and E.N. Walsh; **Inorg. Synth.**, 7, 73 (1963).

131. T. Wieland and H. Bernard; **Ann.**, 572, 190 (1951).

132. E. Breuer, R. Karaman, H. Leader, A. Goldblum and R. Moshe; **Phosphorus and Sulfur**, 30, 113 (1987).

133. E. Breuer; **Private Communication** (1988).

134. B. Fischer and J. Michalski; **Roczniki Chem.**, 26, 688 (1952).

135. Bette Davidowitz and Tomasz A. Modro; **Org. Mass Spectrom.**, 19, 128 (1984).

136. Tomasz A. Modro, Mary A. Lawry and Elaine Murphy; **J. Org. Chem.**, 43, 5000 (1978).

137. B.C. Saunders, H.G. Cook, J.D. Ilett, K.J. Stacey, H.G. Watson, I.G.E. Wilding and S.J.Woodcock; **J. Chem. Soc.**, 2921 (1949).

138. J.E. Gardner and B.A. Kilby; **J. Chem. Soc.**, 1769 (1950).

139. K. Rorig; **J. Am. Chem. Soc.**, 71, 3561 (1949).